Cornell University

Graduate School of Medical Sciences 1991 • 1992

Academic Calendar 1991–92

1991

Orientation for new students	Wednesday and Thursday, August 28 and 29
Opening Exercises	Wednesday, August 28
Registration for Quarter I* and Fall semester**	Thursday and Friday, August 29–30
Labor Day Holiday observed	Monday, September 2
Quarter I and Fall semester begin	Tuesday, September 3
Quarter I ends	Friday, October 25
Examinations for Quarter I	Friday, October 25–Friday, November 1
Registration for Quarter II**	Friday, November 1 and Monday, November 4
Quarter II begins	Monday, November 4
Thanksgiving recess	Thursday and Friday, November 28 and 29
Winter recess: Instruction suspended 5:00 p.m.	Friday, December 20

1992

Winter recess: Instruction resumed 9:00 a.m.	Monday, January 6
Last day for completing requirements for January degrees	Friday, January 10
Quarter II and Fall semester end	Wednesday, January 15
Conferral of January degrees	Wednesday, January 15
Examinations for Quarter II	Thursday, January 16–Friday, January 24
Martin Luther King, Jr's Birthday observed	Monday, January 20
Registration for Quarter III* and Spring semester***	Friday, January 24 and Monday, January 27
Quarter III and Spring semester begin	Monday, January 27
Presidents' Day Holiday observed	Monday, February 17
Quarter III ends	Friday, March 20
Examinations for Quarter III	Monday, March 23–Friday, March 27
Spring recess	Monday, March 30–Friday, April 3
Registration for Quarter IV	Friday, April 3 and Monday, April 6
Quarter IV begins	Monday, April 6
Twelfth Annual Vincent du Vigneaud Memorial Research Symposium; no classes	Tuesday, May 5
Last day for completing requirements for May degrees	Friday, May 15
Memorial Day Holiday observed	Monday, May 25
Commencement Day, conferral of May degrees	Wednesday, May 27
Quarter IV and Spring semester end	Friday, May 29
Examinations for Quarter IV	Monday, June 1–Friday, June 5

Summer Term 1992

Registration for summer research	Monday, June 22
Summer research term begins	Monday, June 22
Summer research term ends	Friday, August 14
Last day for completing requirements for August degrees	Friday, August 21
Conferral of August degrees	Monday, August 24

*for students enrolling in courses.

**for students conducting research only, who are on leave of absence, or are in absentia.

***for students changing from course work to research, who are going on leave of absence, or who are converting to in absentia status.

Note: Courses are taught on a quarterly basis, degrees are granted at ends of the Fall and Spring semesters and of the Summer term. The dates shown in the calendar are subject to change at any time by official action of Cornell University.

In enacting this calendar, the Graduate School of Medical Sciences has scheduled classes on religious holidays. It is the intent of the school that students missing classes due to the observance of religious holidays be given ample opportunity to make up work.

Cornell University

Graduate School of Medical Sciences 1991 • 1992

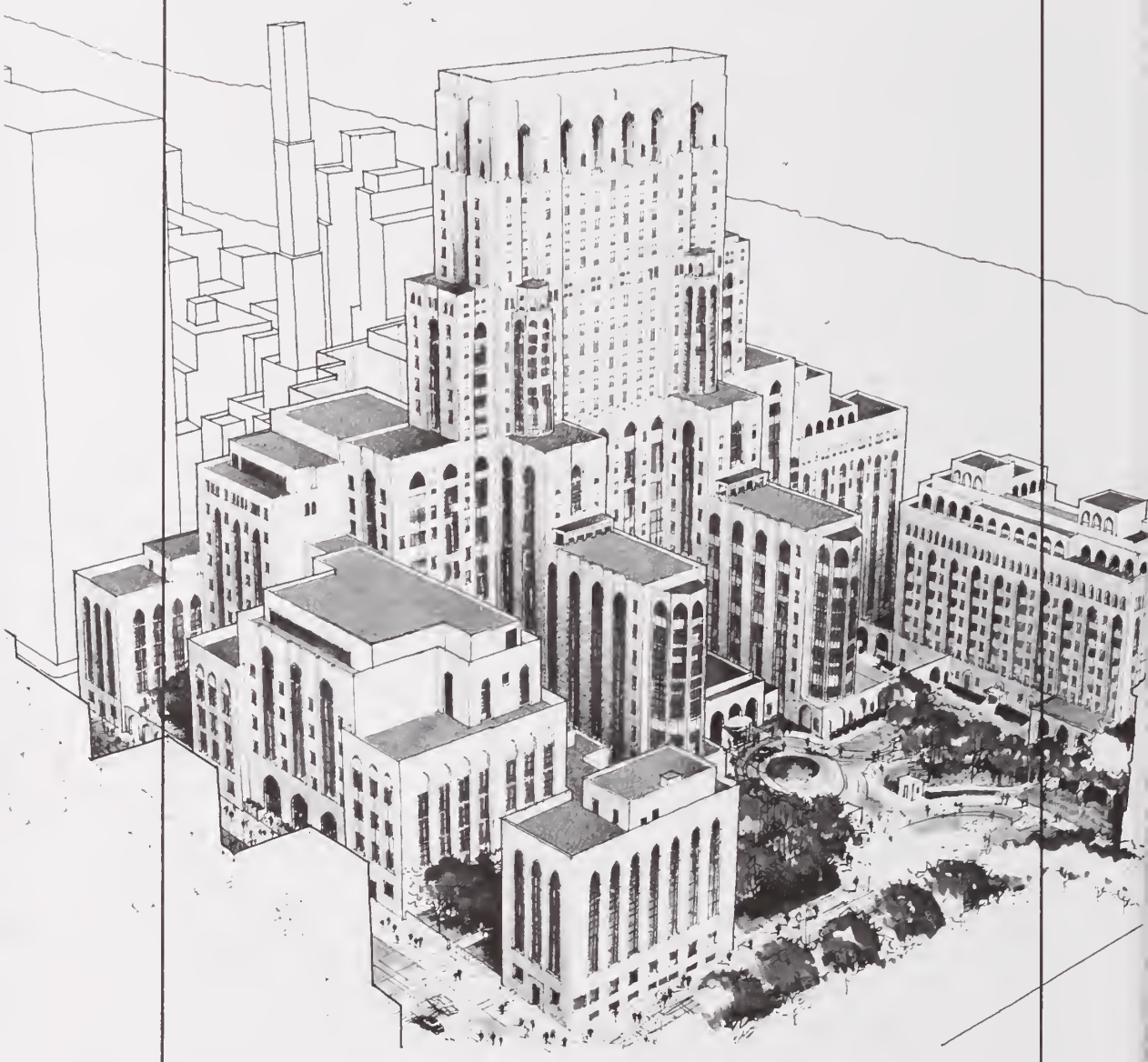
1300 York Avenue, Room A-139
New York, NY 10021
212, 746-6565

Editor/Coordinator: Carolyn B. Schnall

Contents

The courses and curricula described in this Catalog, and the teaching personnel listed herein, are as of July 1, 1991 and are subject to change at any time by official action of Cornell University.

New York Hospital–Cornell Medical Center



Cornell University
Graduate School of Medical Sciences

Purpose

The Graduate School of Medical Sciences, a semi-autonomous component of the Graduate School of Cornell University, provides opportunities for advanced study and research training in specific areas of the biomedical sciences. Graduate training leading to the degree of Doctor of Philosophy is offered by the following programs of study: *Biochemistry, Cell Biology and Genetics, Immunology, Molecular Biology, Neuroscience, Pharmacology,* and *Physiology and Biophysics.* Certain of these fields of study also offer programs leading to the degree of Master of Science. Collaborative programs with Cornell University Medical College lead to the combined degrees of Doctor of Philosophy and Doctor of Medicine.

The faculty of the Graduate School of Medical Sciences recommends the award of advanced general degrees not only as the result of the fulfillment of certain formal academic requirements, but also as evidence of the development and possession of a critical and creative ability in science. Demonstration of this ability is embodied in a dissertation which the candidate presents to the faculty as an original research contribution in the chosen area of study.

A close working relationship between student and faculty is essential to the program of the Cornell University Graduate School of Medical Sciences. Guidance for each student is provided by a Special Committee, a group of at least three faculty members selected by the student. This Special Committee is granted extraordinary independence in working with its student. Other than a broad framework of Graduate School of Medical Sciences requirements for residence, examinations, and a thesis, and additional requirements of the particular field of study chosen by the student, the Special Committee is free to design an individualized program of study with its students. No overall course, credit-hour, or grade requirements are set by the Graduate School of Medical Sciences. A student is recommended for a degree whenever the Special Committee judges the student qualified.

History

The opportunity for graduate study leading to advanced general degrees in the biomedical sciences was first offered at the Cornell University Medical College, in cooperation with the Graduate School of Cornell University, in 1912. In June of 1950, Cornell University, in association with the Sloan-Kettering Institute for Cancer Research, established additional opportunities for graduate study by forming the Sloan-Kettering Division of the Medical College. The resulting expansion of both graduate faculty and research training opportunities on the New York City Campus prompted the organization in January 1952 of the Graduate School of Medical Sciences, composed of two cooperative but separate divisions, known as the Medical College Division and the Sloan-Kettering Division. The Graduate School of Medical Sciences was given full responsibility for advanced general degrees granted for study in residence on the New York City campus of Cornell University.

Facilities

The Cornell University Graduate School of Medical Sciences is part of a large biomedical center extending along York Avenue between 65th and 72nd Streets on Manhattan's East Side. This complex includes Cornell University Medical College, New York Hospital, the Memorial Sloan-Kettering Cancer Center, and The Rockefeller University. The core facilities of the Graduate School of Medical Sciences, which include the research laboratories of its faculty, are located within the Cornell Medical College–New York Hospital complex and the Howard, Kettering, Rockefeller, and Schwartz Laboratory buildings of the Sloan-Kettering Institute for Cancer Research. Other buildings in this area provide student housing and recreational facilities. Several dining rooms and snack bars are located in this complex, and the immediate neighborhood abounds in a large variety of restaurants.

Especially noteworthy are two large biomedical libraries available to graduate students. The smaller of the two, the Medical Library–Nathan Cummings Center, contains over 32,000 books and journals. The Samuel J. Wood Library has a collection of 147,500 volumes and subscriptions to 1,630 journals. It is one of the country's first fully automated medical libraries featuring computer terminals which provide access to library materials and permit bibliographic searches in a number of data bases. A microcomputer center, with an extensive software collection, is maintained at the library for staff and students.

Organization

The faculty of the Graduate School of Medical Sciences is composed of the professional staffs of the basic science and clinical departments of Cornell University Medical College, and the professional staff members of the Sloan-Kettering Institute for Cancer Research.

Graduate training is offered in several areas of the biomedical sciences. These Programs of Study bring together faculty members who have related research and teaching interests.

Executive Committee

The Executive Committee is both the administrative and judicial board of the Graduate School of Medical Sciences and its members have continuing responsibility for the academic affairs of the school. The Committee is composed of the Chairpersons of the graduate programs, the Dean and Associate Dean, the Provost for Medical Affairs of Cornell University, the Director of the Sloan-Kettering Division, the Chairperson and Vice-Chairperson of the Faculty Advisory Committee (see below), and two nonvoting, elected student representatives.

The Executive Committee considers such matters involving the interests and policies of the Graduate School of Medical Sciences as are referred to it by the Faculty Advisory Committee, by individual members of the Faculty, or are generated upon its own initiative. The Committee approves the addition or deletion of programs of study, reviews the admission of students, approves a student's major and minor programs, reviews the curriculum and requirements for degrees.

The Executive Committee is chaired by the Dean, who is the academic administrative officer of the Graduate School of Medical Sciences and is also an Associate Dean of the Graduate School of Cornell University. The Associate Dean, who is also an Assistant Dean of the Graduate School of Cornell University, is the Secretary of the Executive Committee.

Faculty Advisory Committee

The Faculty Advisory Committee is the primary body representing the views of the Faculty of the Graduate School of Medical Sciences. The Committee advises the Dean and the Executive Committee on the impact of educational and policy matters under their consideration and recommends changes in educational activities, procedures, and policy of the Graduate School of Medical Sciences.

The Faculty Advisory Committee is composed of elected faculty representatives from the graduate programs and one elected student representative from each Division. The Chairperson and Vice-Chairperson of the Committee are elected by its membership. Non-voting members are the Dean and Associate Dean, the Provost for Medical Affairs of Cornell University, and the Director of the Sloan-Kettering Division.

Special Programs

Tri-Institutional M.D.-Ph.D. Program

This program offers a small number of highly qualified college graduates the opportunity to study both clinincal and biomedical disciplines leading to the M.D. and Ph.D. degrees. The combination of basic research skills and clinical experience prepares students in the program for teaching and investigative careers. Preclinical and clinical training are provided by the faculty of Cornell University Medical College. Research opportunities are offered in the laboratories of the Cornell University Graduate School of Medical Sciences, The Rockefeller University, and the Sloan-Kettering Institute.

The M.D.-Ph.D. Program offers an intensive and intellectually challenging six-year course of study. Participants spend the first two years as medical students mastering the preclinical sciences and attending research-oriented seminars led by experts in the biomedical fields. The summer months are spent in the laboratory learning experimental techniques and doing research. The students spend the next three years as full-time graduate students, mainly doing laboratory research and writing the thesis. Research training is offered in the following areas: biochemistry, biophysics, cell biology, genetics, immunology, molecular biology, neurosciences, pharmacology, and physiology. The sixth year consists of required clerkships in medicine, surgery, obstetrics and gynecology, pediatrics, neurology, psychiatry, radiology, public health, and anesthesiology. The six-year plan satisfies the minimum residency requirements for both the M.D. and Ph.D. degrees.

A successful applicant will demonstrate excellent undergraduate science preparation and a strong commitment to combining an investigative career in the biomedical sciences with clinical medicine. Applicants must satisfy the requirements of each institution. All students accepted in the M.D.-Ph.D. Program receive full-tuition scholarships and stipends to cover living expenses for the six-year period.

For application to the M.D.-Ph.D. Program, see p. 66.

Ph.D.-M.D. Program

Students enrolled in the Graduate School of Medical Sciences may be eligible for admission into the Ph.D.-M.D. Program, jointly sponsored by the Medical College and the Graduate School of Medical Sciences. This program is designed for those graduate students who find that their teaching and research goals require the acquisition of the M.D. degree in addition to the Ph.D. degree. The program is *not* designed as an alternate path for students who have the M.D. degree as their primary goal, but who have not been accepted by a medical school. Those who know, at the time of application to Cornell, that they want to pursue a course of study leading to both degrees should apply to the M.D.-Ph.D. program described above.

See p. 66 for application and graduation requirements of the Ph.D.-M.D. program.

Faculty and Research Activities

Biochemistry

Faculty

Mary E. Anderson
John P. Blass
Adele I. Boskey
Esther M. Breslow
Arthur J. L. Cooper
Gordon F. Fairclough
Jerald D. Gass
Jack Goldstein
Owen W. Griffith
David P. Hajjar
Rudy H. Haschemeyer
Bernard L. Horecker (Emeritus)
Alton Meister
Ursula Muller-Eberhard
Abraham Novogrodsky
Julian R. Rachele (Emeritus)
Hugh D. Robertson
Albert L. Rubin
Edward T. Schubert
Richard I. Soffer
Kurt H. Stenzel
Suresh S. Tate
Sidney Udenfriend
Daniel Wellner
David Zakim

Research Activities

Members of the Biochemistry program are engaged in research spanning a wide spectrum of scientific areas in which a variety of modern techniques of molecular biology and chemistry are used. *Dr. Meister*'s research is concerned with the study of enzymes, especially those involved in amino acid and peptide metabolism. The research involves isolation of enzymes, determination of their structures and properties, cloning, sequencing and expression. The research is basic in nature, but significant relationships between this research and human disease have been discovered and are also being explored. Current work involves the metabolism and function of glutathione, including the relationships of this tripeptide to transport, metabolism, radiation, chemotherapy, and the functions of mitochondria and cells of the immune system.

Dr. Anderson's research involves the synthesis of compounds which increase or decrease cellular glutathione levels. These inhibitors or prodrugs are used *in vitro, in vivo,* or in culture to study the metabolism and function of glutathione. Enzyme studies include cloning, expression and site-specific mutagenesis to examine enzyme mechanisms. Recent research interests include the mechanisms of T-lymphocyte activation of multi-drug resistance, and the effects of viral infection on glutathione metabolism.

Dr. Blass's research focuses on the neurochemistry of disease, and specifically on the cellular and molecular neurobiology of Alzheimer's disease. His laboratory concentrates on the use of cell culture models, including cultures developed in his laboratory from autopsy human brain. These models are used to study regulation and other dynamic aspects of cellular function which cannot be studied in autopsy brain.

Dr. Boskey's research is concerned with elucidating the factors controlling physiologic and dystrophic calcification. Hydroxyapatite formation and growth are studied in solution, collagen gels, in animal tissues, and in cell culture. Recent studies have concentrated on the mechanism of action of proteoglycans (a mineralization inhibi-

Views of Manhattan from Cornell Medical College.

tor) and phosphorylated matrix proteins (promoters of mineralization). Studies are also in progress on: the role of vitamin D metabolites in bone lipid metabolism, the actions of other matrix proteins in the regulation of calcification, and the effect of trace elements on bone metabolism.

Dr. Breslow is concerned with understanding the forces that determine the specificity of protein-protein interactions and the relationship between protein structure and function. She has been studying the interactions of the pituitary peptide hormones, oxytocin and vasopressin, with their storage protein, neurophysin. These studies are directed towards elucidating the binding site regions of the hormones and of the protein and at quantitating the energies of different components of the interaction. A second area of research concerns the mechanism by which proteins are degraded intracellularly during normal protein turnover. The aims of these studies are to understand the precise role of ubiquitin, a small protein known to be involved in this process, and to elucidate the mechanisms underlying the selection of proteins for degradation.

Dr. Cooper's laboratory is working in the area of α-keto acid biochemistry and pyridoxal phosphate enzymes. Another area of active research is the metabolism of amino acids and ammonia in the brain and other tissues. For this purpose, molecules labeled with short-lived positron-emitting isotopes are synthesized and their distribution in tissues is analyzed by various techniques including positron emission tomography. Cerebral energy metabolism, with particular emphasis on the malate-aspartate shuttle and its disruption in various disease states are also being investigated. *Dr. Cooper* is also working on the design of specific enzyme inhibitors of two metabolically important enzymes, namely aspartate aminotransferase and lactate dehydrogenase. His group has isolated and is studying the molecular biology of an enzyme implicated in the bioactivation of certain nephrotoxic/cerebrotoxic halogenated compounds.

Dr. Goldstein is studying the structure and function and erythrocyte surface antigens and is working on enzymatic methods for the removal of immuno-dominant sugars responsible for blood group A and B activity. He is also isolating and characterizing proteins exhibiting Rh structures, clarification of the genetic systems involved in Rh expression and modification of such antigenic sites by chemical and enzymatic procedures.

Dr. Griffith's research involves the design, synthesis and utilization *in vivo* of enzyme-selective inhibitors and substrates. These compounds are used both to evaluate and to control the metabolic flux through various pathways in intact animals. Recent studies have focused on the manipulation of glutathione, cysteine, nitric oxides and carnitine-dependent metabolisms. Enzyme-selective inhibitors were developed that allow either glutathione biosynthesis and utilization to be blocked; techniques allowing extracellular cystine formation to be controlled were also developed. The inhibitors were shown to be useful in treating animal trypanosomiasis, enhancing oxidative killing of tumor cells, and preventing the formation of leukotriene C. New inhibitors have also been developed to allow *in vivo* control of carnitine metabolism. Applications of these compounds include the investigation and therapy of inherited diseases of lipid metabolism and diabetes. In collaboration with Drs. Gross and Levi (Pharmacology) and Dr. Nathan (Medicine) inhibitors have been developed that allow nitric oxide synthesis by macrophages and endothelial cells to be selectively controlled. Such inhibitors are being used in studies of septic shock, blood pressure regulation, and immune cell-mediated killing of tumor cells.

Dr. Hajjar's laboratory has focused on cell-cell and cell-virus interactions during the pathogenesis of arteriosclerosis. Studies are aimed at elucidating the cellular mechanisms by which viruses and chemical mutagens alter gene expression that would modify the structural state of arterial lipid in such a manner as to render immobilized lipid. In addition, studies are underway to determine the mechanism of the cellular portal of entry of herpes virus into mammalian cells. Techniques used in the laboratory include transcriptional and translational assays to define gene regulation during arterial injury, and differential scanning calorimetry and mass spectroscopy to characterize the physical state of the arterial lipids.

Dr. Haschemeyer's laboratory concentrates on the development of physical methods to study molecular structure and interactions. Current emphasis is directed toward computer modeling of biological flow methods and heterogeneous-phase reactions. Additional computer applications are directed toward defining prognostic factors and treatment protocols that optimize graft survival in kidney transplant patients.

Dr. Muller-Eberhard is investigating the mechanisms of transport of iron protoporphyrin IX and its metabolic precursors by proteins in the blood stream as well as within hepatocytes. She is studying the exchange of porphyrins between proteins purified from serum and from hepatocytes; developing methods which delineate the function of these proteins in the delivery of porphyrins to hepatocytes and their intracellular distribution; and assessing the interaction of these proteins with artificial and biological membranes to learn how they may facilitate ligand transport across cellular and intracellular barriers.

Dr. Robertson's work involves the structure and function of biologically important RNA molecules. Recent work has focused on RNA-catalyzed cleavage of viroid-like RNA pathogens during their replication. For example, a region of the genomic RNA of the delta hepatitis agent has been isolated and found to contain a highly active RNA enzyme ("ribozyme") region. Work on RNA processing and replication of viroid-like agents and their replication by rolling circle mechanisms, and a 2-domain model for the structure of the delta hepatitis RNA genome, structural probe for RNA tertiary structure at or near biologically active sites involving ultraviolet light-induced cross-linking and mapping by direct techniques of the resulting new covalent linkages.

The main objective of *Dr. Soffer*'s research is to characterize the physical, chemical, and biochemical properties of angiotensin II receptor which has been purified to a nearly homogeneous state from rabbit hepatic membranes.

Drs. Stenzel and Novogrodsky are interested in determining mechanisms involved in the regression of metastatic kidney tumor mediated by autologous killer cells activated by the oxidizing mitogens and recombinant interleukin 2 (rIL2). They are using *in vitro* systems to determine mechanisms of cell mediated cytotoxicity. These investigations include an analysis of mononuclear cell sub-populations involved, mechanisms of target cell lysis (membrane structures *vs.* soluble factors), target specificity, and synergistic effects of additional biologic response modifiers. *In vivo* systems are used to determine mechanisms of tumor lysis *in vivo* mediated by administration of activated killer cells and rIL2 in mouse tumor models. Clinical studies are underway in patients with metastatic renal cell carcinoma to determine efficacy and toxicity of adoptive immunotherapy. Alterations in patients' immune responses are determined. These studies include a structural and functional analysis of circulating mononuclear cell populations.

Dr. Tate is investigating the molecular basis of amino acid transport in animal cells. It has long been known that amino acids are transported into mammalian cells by a number of carrier-mediated systems, some of which are energized by a sodium gradient while others are sodium-independent. In the case of nutritionally essential amino acids the uptake processes become vital for the survival of the cells. Little, however, is known about these catalysts at a molecular level. Research in the laboratory is aimed at the molecular characterization of neutral amino acid transporters. The cDNAs encoding these transporters are being cloned using the *Xenopus* oocyte expression system for screening of the cDNA libraries.

Dr. Wellner's laboratory is concerned with the structure and function of enzymes involved in amino acid metabolism, such as L-amino acid oxidase and threonine deaminase. Techniques employed for the study of protein structure include amino acid analysis and microsequencing using a gas-phase protein sequencer.

Recent Publications

Anderson, M. E. (with Meister, A.), Glutathione monoesters, *Analytical Biochemistry* 183:16–20, 1989.

Anderson, M. E. (with Suthanthiran, M., Sharma, V. K., and Meister, A.), Glutathione regulates activation-dependent DNA synthesis in highly purified normal human T lymphocytes stimulated via the CD2 and CD3 antigens. *Proc. Natl. Acad. Sci. U.S.A.* 87:3343–3347, 1990.

Anderson, M. E. (with Kalebic, T., Kinter, A., Poli, G., Meister, A., and Fauci, A. S.), Suppression of HIV expression in chronically infected monocytic cells by glutathione, glutathione ester, and N-acetyl cysteine. *Proc. Natl. Acad. Sci. U.S.A.*, 88:986–990, 1991.

Boskey, A. L., Hydroxyapatite formation in a dynamic gel system: Effects of Type I collagen, lipids, and proteoglycans, *J. Phys. Chem.* 93:1628–1633, 1989.

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Breslow, E. (with Burman, S., Wellner, D., Chait, B., and Chaudhary, T.), Complete assignment of neurophysin disulfides indicates pairing in two separate domains. *Proc. Natl. Acad. Sci. U.S.A.* 86:429–433, 1989.

Breslow, E. (with Bamezai, S., and Banez, M.A.T.), Structural and functional changes associated with modification of the ubiquitin methionine. Biochemistry 29:5389–5396, 1990.

Breslow, E. (with Burman, S.), Molecular, thermodynamic and biological aspects of recognition and function in neurophysin-hormone systems: A model system for the analysis of protein-peptide interactions, *Adv. Enzymol.* 63:1–67, 1990.

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Cooper, A. J. L. (with Lai, J. C. K., Murthy, C. R. K., Hertz, E., and Hertz, L.), Differential effects of ammonia and β-methylene-DL-aspartate on metabolism of glutamate and related amino acids by astrocytes and neurons in primary culture. *Neurochem. Res.* 14:377–389, 1989.

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Goldstein, J. (with Lenny, L., Davies, D., and Voak, D.), Further evidence for the presence of A antigen on group B erythrocytes through the use of specific exoglycosidase. *Vox Sang.* 57:142–146, 1989.

Goldstein, J. (with Suyama, K.) Enzymatic evidence for difference in the placement of Rh antigens within the red cell membrane. *Blood* 75:255–260, 1990.

Goldstein, J. (with Lenny, L. L., Hurst, R., Benjamin, L. J., and Jones, R. L.), Single-unit transfusions of RBC enzymatically converted from group B to group O to A and O normal volunteers. *Blood* 77:1383–1388, 1991.

Griffith, O. W. (with Kilbourne, R. G., Gross, S. S., Jubran, A., Adams, J., Levi, R. and Lodats, R. F.), N^G-Methyl-L-arginine inhibits tumor necrosis factor-induced hypotensin: Implications for the involvement of nitric oxide. *Proc. Natl. Acad. Sci. U.S.A.* 87:3629–3632, 1990.

Griffith, O. W. (with Gross, S. S., Stuehr, D. J., Aisaka, K., Jaffe, E. A., and Levi, R.), Macrophage and endothelial cell nitric oxide synthesis: Cell-type selective inhibition by N^G-aminoarginine, N^G-nitroarginine and N^G-methylarginine. *Biochem. Biophys. Res. Commun.* 170:96–103, 1990.

Griffith, O. W. (with Friedman, H. S.), Inhibition of metabolic drug inactivation: Modulation of drug activity and toxicity by perturbation of glutathione metabolism. *in:* Syncrgism and Antagonism in Chemotherapy (T.-C. Chou and D. C. Rideout, eds.), Academic Press, New York. pp. 245–284, 1991.

Hajjar, D. P. (with Baird, A., Florkicwicz, R. Z., and Kaner, R. J.), Mediation of virion penetration into vascular cells by association of basic fibroblast growth factor with herpes simplex virus. *Nature* 348:344–346, 1990.

Hajjar, D. P. (with Etingin, O. R. and Silverstein, R. L.), Viral activation of the coagulation cascade: Molecular interactions at the surface of infected endothelial cells. *Cell* 61:657–662, 1990.

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Meister, A. (with Yan, N.), Amino acid sequence of rat kidney γ-glutamylcysteine synthetase, *J. Biol. Chem.*, 265:1588–1593, 1990.

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Robertson, H. D. (with Branch, A. D., Benenfeld, B. J., Baroudy, B. M., Wells, F. V., and Gerin, J. L.), An ultraviolet-sensitive RNA structural element in a viroid-like domain of the hepatitis delta virus, *Science* 243:649–652, 1989.

Soffer, R. L. (with Kiron, M. A. R.), Purification and properties of a soluble angiotensin II-binding protein from rabbit liver. *J. Biol. Chem.*, 264:4138–4142, 1989.

Tate, S. S. (with Urade, R., Getchell, T. V., and Udenfriend, S.), Expression of the mammalian Na^+-independent L system amino acid transporters in *Xenopus laevis* oocytes, *Arch. Biochem. Biophys.*, 275: 591–596, 1989.

Tate, S. S. (with Urade, R., Micanovic, R., Gerber, L., and Udenfriend, S.), Secreted alkaline phosphatase: An internal standard for expression of injected mRNAs in the *Xenopus* oocyte, *FASEB J.*, 4:227–231, 1990.

Udenfriend, S. (with Berger, J., Micanovic, R., and Greenspan, R.), Conversion of placental alkaline phosphatase from a phosphatidylinositol-glycan-anchored protein to an integral transmembrane protein. *Proc. Natl. Acad. Sci. U.S.A.* 86:1457–1460, 1989.

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Wellner, D. (with Stole, E., Seddon, A. P., and Meister, A.), Identification of a highly reactive threonine residue at the active site of gamma-glutamyl transpeptidase. *Proc. Natl. Acad. Sci. U.S.A.* 87:1707–1709, 1990.

Cell Biology and Genetics

Faculty

Rosemary F. Bachvarova
David M. Bader
Robert Benezra
June L. Biedler
Anthony M. C. Brown
Michael A. Caudy
Raju S. K. Chaganti
Moses V. Chao
Sandra Citi
Jacques Cohen
Paul J. Deutsch
David B. Donner
Donald A. Fischman
Leonard P. Freedman
James L. German III
Marvin C. Gershengorn
David P. Hajjar
Franz-Ulrich Hartl
Eric A. Jaffe
Maria Jasin
Irwin L. Klein
Eseng Lai
Paul A. Marks
Joan Massagué
Malcolm A. S. Moore
Ralph L. Nachman
Carl F. Nathan
Joel D. Pardee
Marilyn D. Resh
Richard A. Rifkind
Hugh D. Robertson
Enrique Rodriguez-Boulan
James E. Rothman
Roy L. Silverstein
Martin Sonenberg
Lisa Staiano-Coico
Paula Traktman
Perrin C. White
Martin Wiedmann
David Zakim

Research Activities

The faculty of the Interdivisional Program in Cell Biology and Genetics conduct research in a broad range of fields which include the most exciting areas of genetics and cell, developmental and molecular biology. Specific interests include the developmental biology of the early embryo and of cardiovascular and muscle tissues; membrane biology; cell motility and the cytoskeleton; the molecular biology of cell growth, differentiation and oncogenic transformation; endocrinology and hormone receptors; human somatic cell and cyto-genetics; molecular virology. These studies are pursued using the most current cell biological, genetic, molecular and immunological methodologies in modern and well-equipped facilities.

Dr. Bachvarova is interested in gene expression in early mouse embryos and germ cells. Current projects under investigation include: the control of translation of endogenous and injected mRNAs during meiotic maturation of mouse oocytes, the expression of genes encoding growth factors that may be involved in mesoderm induction, and the expression of c-*kit,* a tyrosine kinase receptor involved in germ cell development. *Dr. Bader*'s laboratory is concerned with the development of the heart. Specific interests are the differential expression of myosin heavy chains in the developing myocardium, and the mechanisms by which myocardial heterogeneity are generated. Monoclonal antibody and recombinant DNA technologies provide the basis for these studies of cardiac myogenesis *in vivo* and *in vitro. Dr. Benezra*'s research is

focused on the newly discovered Id protein, a functional antagonist of the helix-loop-helix class of transcriptional activators. His interest is in the role of this transcriptional repressor in embryonic development and muscle differentiation. *Dr. Biedler*'s research concerns the genetic mechanisms underlying the cellular acquisition of multiple resistances to cancer chemotherapeutic agents. At least two amplified genes with a role in this process have been identified and are being studied. A second area of research is human neuroblastoma, a system involving amplification of a specific gene and consequent cytogenetic abnormalities. Current studies are focused on the correlation of the differential expression of the N-myc oncogene and the EGF receptor gene with varying states of malignant transformation and/or cell differentiation.

Dr. Brown is studying the molecular mechanisms of oncogene action in neoplasia and the function of proto-oncogenes in normal cells. A major focus of his research is the proto-oncogene *int*-1 *(wnt-1),* which plays an important role in the formation of mouse mammary carcinomas and is strongly implicated in early embryonic development of the nervous system. Analyses of other members of the *wnt* family and their developmental roles are also underway. *Dr. Caudy* is interested in the molecular genetic mechanisms which control neuronal pattern formation during development. A network of cell determination genes which control neuronal cell fate in *Drosophila* embryos are the major focus of his laboratory. The proteins encoded by this gene family are members of the helix-loop-helix class of transcription factors, whose mammalian homologues are proto-oncogenes. The major aim of *Dr. Chaganti*'s research is to define the role played by hereditary factors in the etiology and progression of human malignancy. Studies focus on inherited changes associated with cancer predisposition and with acquired changes associated with various tumors. Chromosomal rearrangement, gene amplification, point mutation and gene deregulation are considered. *Dr. Chao*'s research interests focus on gene expression and regulation in mammalian cells. Molecular genetic techniques are being applied to study the gene encoding the nerve growth factor receptor and to analyze the role of the receptor in the mechanism of signal transduction by NGF and in the development of the nervous system.

The focus of *Dr. Citi*'s research is the structure of tight junctions, which are critical for epithelial cell function. Biochemical and molecular genetic analysis of cingulin, a specific tight junction protein, is being undertaken to understand its role in the junction. A variety of research areas with relevance to human *in vitro* fertilization are the focus of the work in *Dr. Cohen*'s laboratory. These include the development of improved micromanipulations which aid sperm in crossing the zona pellucida as well as approaches to correcting polyspermic embryos. Embryo co-culture and preimplantation genetic diagnosis are also topics of interest. *Dr. Deutsch*'s laboratory studies the mechanisms whereby hormones and their second messengers induce gene expression. Regulation of collagenase gene expression via a cAMP-responsive and phorbol ester-responsive DNA motif is a current focus of research. *Dr. Donner* is studying the molecular basis for signal transduction through peptide hormone and cytokine receptors. A major focus of present research is the structure, function and regulation of the receptor for tumor necrosis factor. *Dr. Fischman's* research focuses on the cell and molecular biology of skeletal and cardiac muscle development. The identification of genes encoding novel muscle components, retroviral analysis of cell lineages, and targeted gene insertions are being employed to better define the steps involved in sarcomere assembly.

Dr. Freedman's laboratory is attempting to elucidate the molecular mechanisms by which DNA binding proteins effect differential gene expression. His work is centered on the study of transcription factors containing the important zinc finger motif

and their direct role in mediating regulatory events which control development and differentiation. Several clinically relevant aspects of human genetics are under study in *Dr. German*'s laboratory. The primary defect in Bloom's syndrome is being mapped with the eventual goal of cloning the gene involved; this syndrome illustrates the developmental consequences of somatic mutation. The molecular dissection of the pseudoautosomal and adjoining regions of human sex chromosomes is also an area of research interest. The focus of research in *Dr. Gershengorn*'s laboratory is the delineation of the mechanisms of signal transduction used by throtropin-releasing hormone (TRH) in pituitary cells. Using a recently isolated cDNA for the TRH receptor, the molecular details of TRH binding, of coupling to a G protein that activates inositol lipid hydrolysis and of receptor regulation will be studied. Research in *Dr. Hajjar's* laboratory focuses on the cellular portal of entry of herpesvirus and the role these viruses may play in the activation of the coagulation cascade on the surface of the blood vessel wall and the atherosclerotic process. *Dr. Hartl*'s laboratory is interested in the mechanisms and components involved in the folding of newly-synthesized proteins. The lab is presently investigating the molecular mechanism of catalyzed protein folding.

Dr. Jaffe is studying stimulus-response coupling, signal transduction, and prostacyclin production in endothelial cells. Current research includes expression cloning of the human endothelial cell thrombin receptor using the *Xenopus laevis* oocyte system. Cytokine-induced expression of endothelial cell surface antigens is also being studied. The focus of *Dr. Jasin*'s work is the development of methods to precisely modify the mammalian genome by recombination. The mechanism by which mammalian cells achieve homologous recombination is also of interest. *Dr. Klein* is studying the effects of cardiac contractility and thyroid hormone on the regulation of cardiac myosin synthesis. The control and maintenance of cellular differentiation, and the mechanism of hormone action, are the two major interests of *Dr. Lai.* The approaches taken in the laboratory include the identification and analysis of liver-specific genes and the study of genes which are rapidly induced by growth hormone. Of major interest to *Drs. Marks and Rifkind* are the cellular and molecular mechanisms that control coordinated gene expression and proliferation during induced cell differentiation. The principal experimental model is the murine erythroleukemia cell (MELC), which is a virally transformed red blood cell precursor arrested at a stage of the lineage called the colony-forming cell for erythropoiesis. A number of defined chemical agents can induce MELC to express the genetic program of erythroid differentiation. Present studies address the signal mechanisms triggered by inducing agents, the mechanism of induced gene expression, and the identification and cloning of genes implicated in the programmed cessation of cell proliferation.

Dr. Massagué investigates the mediation of intercellular communication by growth and differentiation factors. Much of the research is centered on understanding the activities of transformation growth factors (TGF). *Dr. Moore*'s research concerns the mechanism of action of hematopoietic growth factors and interleukins in regulating the proliferation and differentiation of normal and leukemic hematopoietic stem cells. The regulation of factor production and the modulation of receptors on various cell populations are being analyzed; *in vivo* tumor models are being investigated to test the potential for cytokine treatment in intensified chemotherapy. The focus of work in *Dr. Nachman*'s laboratory is the endothelial cell membrane and the macromolecular assembly of fibrinolytic constituents that influence vascular non-thrombogenicity. *Dr. Nathan*'s efforts are aimed at understanding how phagocytic leukocytes kill microbes, tumor cells, and normal host elements at inflammatory sites. Investiga-

tions into the biochemical bases of cytotoxicity by macrophages and granulocytes are integrated into a context of cell biology and clinical investigation. *Dr. Pardee*'s research is concerned with the regulation of the actin cytoskeleton by actin-binding proteins. Regulatory proteins, such as myosin, severin and an actin filament bundling factor, have been isolated and are being analyzed for their roles in cell migration and neoplastic transformation.

The focus of *Dr. Rodriguez-Boulan*'s laboratory is the regulation of the normal and the transformed epithelial cell phenotype. The roles of protein targeting, the cytoskeleton, and regulatory signals and growth factors are studied using biochemical, immunological, virological and molecular techniques in combination with modern video and electron microscopy procedures. *Dr. Robertson*'s research is focused on structural and functional analysis of biologically important RNA molecules. RNA genomes of viroid-like organisms such as the hepatitis delta agent are a current focus of interest. The work in *Dr. Rothman*'s laboratory is focused on intracellular protein sorting. An *in vitro* transport system derived from Golgi stacks has been developed; this system allows a biochemical analysis of protein sorting and the associated protein modifications. Biochemical analysis of one factor (NSF) essential for the transport process is underway. The interaction of various cytoplasmic oncoproteins with membrane receptors is the major interest of *Dr. Resh's* laboratory. The laboratory is investigating the association of the myristylated *src* protein with the plasma membrane, an association which is necessary for *src*-mediated neoplastic transformation. Two main areas of research are the identification of the myristyl-src receptor and the enzymology of protein myristylation. *Dr. Silverstein's* interests concern the events that occur on the surface of platelets and vascular cells during thrombosis and atherosclerosis. His laboratory is pursuing a molecular biological analysis of proteins expressed preferentially on the surface of activated platelets, as well as examining relevant features of cell-cell and cell-matrix adhesion.

Dr. Sonenberg's long-range objective is the molecular description of membrane transduction of peptide hormonal messages after interaction with a specific membrane receptor or other membrane component. *Dr. Staiano-Coico*'s research focuses on investigating the regulation of growth and differentiation of epithelial cells. The laboratory employs a number of molecular, biochemical and flow cytometric techniques to characterize the changes which epithelial cell subpopulations undergo during transition to a terminally differentiated state. The main focus of *Dr. Traktman*'s research is a molecular genetic analysis of vaccinia virus. Of particular interest are the temporal regulation of gene expression and the coordination of viral DNA replication. A variety of molecular, genetic and biochemical techniques are being employed to identify and characterize the viral genes and enzymes involved in DNA replication, recombination, and the maintenance of DNA topology. A new area of research within the laboratory is a molecular genetic and cell biological investigation of the initiation and maintenance of bone cell differentiation. *Dr. Wiedmann*'s laboratory is interested in the mechanism of protein translocation across membranes. His lab is currently attempting to reconstitute translocation with the purified SSR complex and other necessary components. *Dr. White*'s laboratory studies molecular defects associated with inherited disorders of steroid metabolism, and is elucidating the mechanisms by which these disorders affect growth, sexual differentiation and blood pressure homeostasis. The main interest of *Dr. Zakim*'s laboratory is solvent-solute interactions in membranes, in which the polymethylene chains are the solvent and proteins or small apolar molecules are the solutes. A major emphasis is on how these non-specific effects regulate the functions of integral membrane proteins.

Recent Publications

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Immunology

Faculty

Anthony P. Albino
Nicholas Chiorazzi
Bo Dupont
Ulrich Hämmerling
Alan Houghton
Janet S. Lee
Kenneth O. Lloyd
Henry W. Murray
Carl F. Nathan
Janko Nikolic-Zugic
Abraham Novogrodsky
Herbert F. Oettgen
Lloyd J. Old
Richard J. O'Reilly
David N. Posnett
Wolfgang Rettig
Carlo Russo
Rise Schwab
Gregory W. Siskind
Kurt H. Stenzel
Osias Stutman
Marc E. Weksler
Soo Young Yang

Research Activities

The main interests of the Immunology faculty are focused on the complex molecular and cellular mechanisms responsible for the development and regulation of the immune system. Research programs can be grouped into three main areas: (1) immunogenetics of cell surface molecules involved in the differentiation and function of normal and malignant lymphoid cells; (2) cellular immunology of the interactions between cells and their secreted products, and (3) tumor immunology of the transformed tumor cell and its host, aimed at designing possible diagnostic and therapeutic strategies. Research in all three areas involves studies using both animal models and human cells. Immunology is multidisciplinary in its approaches and has generated its own methodology (such as the production of monoclonal antibodies, and the continuous *in vitro* growth and cloning of lymphoid cells), in addition to using the methods of other disciplines, including biochemistry and molecular biology. For example, the analysis of the biological significance of a given lymphoid cell surface antigen is not only studied using classical genetics and in functional assays using monoclonal antibodies, but also by isolating the molecule and defining its structure using biochemical techniques and characterizing its gene with the tools of molecular biology. Thus, the general approach of the research program is to define immunological events at the biological, biochemical and molecular levels.

In the field of tumor immunology, *Dr. Albino*'s laboratory is examining the role of specific oncogenes in the pathogenesis of malignant melanoma and renal carcinoma. This includes a comprehensive study of the steps required for the transformation of human melanocytes and proxymal tubule cells. In addition, this laboratory also studies the structure and function of melanoma cell-surface differentiation proteins and their gene sequences.

Dr. Chiorazzi's laboratory is investigating the mechanisms and cellular interactions involved in B lymphocyte activation and differentiation to antibody secreting cells. Studies of selected lymphoid cell surface receptors and their ligands are integral

components of these analyses. Monoclonal populations of lymphoid cells, derived by either Epstein-Barr virus transformation or somatic cell hybridization, are frequently employed in this approach. Structural and functional studies of antibodies produced in certain autoimmune disorders have provided basic clues to the relationship between normal and disease states. Autoimmune and allergic disorders as well as the chronic lymphoid malignancies are this laboratory's clinical interests.

The central themes for *Dr. Dupont*'s laboratory are the characterization of the genetic composition of the genes of the human major histocompatibility complex (MHC); the investigation of the molecular genetic basis for the expression of these extensive genetic polymorphisms of the MHC-encoded cell surface antigens as detected in the population; and the biological role of MHC gene products in immunoregulation and other biological functions. The laboratory is also involved in investigations in the area of transplantation immunology, particularly in relation to the understanding of mechanisms responsible for graft vs. host disease.

For the mouse, the majority of genes encoding lymphocyte antigens are organized in distinct multigene families positioned on several chromosomes. Study of these gene clusters continues to be the major theme of *Dr. Hämmerling*'s efforts. The immunogenetics of murine and human lymphoid and hemopoietic cell surface antigens using monoclonal antibodies is another area of Dr. Hämmerling's studies, with special emphasis on their role in T cell activation.

Dr. Houghton's research program is investigating the expression and regulation of antigens by human tumor cells. Genes coding for these antigens are being identified, sequenced and expressed. The role of differentiation and malignant transformation in the expression of these antigens is an area of active study. Antigens on tumor cells that are potential targets for recognition by the immune system are of particular interest.

The molecular genetics of the human major histocompatibility complex or HLA genes is the major area of study of *Dr. Lee*'s laboratory. Her goals are to identify and characterize genes and their products that govern the tissue specific expression of class II genes. These studies involve the analysis of defects in expression of mutant cell lines derived from immunodeficiency patients. In addition, the laboratory is investigating regulatory polymorphisms associated with different alleles.

Investigations of the glycoproteins and glycolipids of human tumor cells and normal cells are the focus of research in *Dr. Lloyd*'s laboratory. Particular emphasis has been placed on the biochemical identification and characterization of these components.

Dr. Murray has several inter-related research interests. These include (1) macrophage activation for antimicrobial activity, (2) intracellular infections caused by *Toxoplasma gondii* and *Leishmania donovani,* (3) interferon-gamma, and (4) the AIDS T cell defect.

Dr. Nathan's efforts are aimed at understanding how phagocytic leukocytes kill microbes, tumor cells, and normal host elements at inflammatory sites. Investigations into the biochemical bases of cytoxicity by macrophages and granulocytes are integrated into a context of cell biology and clinical investigation.

The focus of *Dr. Nikolic-Zugic*'s laboratory is on the ontogeny of T cells and their differentiation in the thymus. This laboratory is also investigating the interaction of the major histocompatibility complex (MHC) encoded molecules and the TCR during the positive selection of T cells in the thymus.

Dr. Novogrodsky's research interests include mechanisms of lymphocyte activation, oxidative mitogenesis and effector mechanisms mediated by mononuclear cells and cytokines. Current work involves the mitogenic properties of hemin and its analogs and other iron-containing agents (the ferro-mitogens), and the evaluation of their immune stimulatory and anti-tumor activity.

The main effort in *Dr. Oettgen*'s laboratory is on the serological analysis of human cancer antigens, the humoral and cellular immune responses to human cancer, and the development and application of human cancer therapies using immunogenic cancer vaccines, monoclonal antibodies, and cytokines.

Dr. Old's research is concerned with the development of two new approaches to cancer therapy: tumor necrosis factor (TNF) and monoclonal antibodies directed against surface determinants on malignant cells. The latter is part of a general effort to analyze the cell surface of human and murine tumors, with the aim to characterize the important surface molecules, mostly with monoclonal antibodies and other serological procedures.

The principal objective of *Dr. O'Reilly*'s Bone Marrow Transplantation Program is the development and improvement of transplantation approaches for the treatment of lethal disorders of the blood system through an integrated program of clinical and basic research in immunology, hematology, genetics, and transplantation biology.

Dr. Posnett's laboratory is interested in basic problems of immunology. The approach is primarily molecular. The topics under study include the human T cell antigen receptor and several lymphocyte membrane molecules that may serve as lymphokine receptors. In the former case he is interested in understanding the process of antigen/MHC recognition by T cells. Studies are focusing on T cell antigen receptor V gene usage and its relationship with antigen/MHC reactivity. Also of interest are disease associations with the T cell antigen receptor genes. He is also cloning the genes of several putative lymphokine receptors. These studies are aimed at understanding the function of these membrane activation antigens.

The main objective of *Dr. Rettig*'s research is to define the rules and molecular mechanisms by which intrinsic genetic differentiation programs, extrinsic differentiation signals, and malignant transformation are integrated in specific cell types to generate the complex cell-surface patterns seen in human tumors.

Dr. Russo's research is concerned with the role of MHC molecules in the regulation of the immune response. Two major areas are under investigation: (1) the dual function of MHC class II molecules in the induction of self-tolerance and in the biology of the autoreactive T-cell network, (2) the relationship between selective loss of MHC class I molecules by tumor cells and tumor progression.

Dr. Schwab's research focuses on age-associated changes in the activation signal transduction mechanism via the T-cell receptor CD3 complex and IL-2 receptor.

Dr. Siskind is concerned with factors regulating the immune response. In particular, he is studying (1) the role of idiotype anti-idiotype interactions in determining clonal expression and (2) the role of T cells bearing receptors for the Fc of IgD in regulating the magnitude of the immune response.

Dr. Stenzel's studies have focused on biochemical mechanisms of lymphocyte activation, transplantation immunology and the role of cell mediated cytotoxicity in the control of cancer growth. The latter studies include both basic and clinical investigation of adoptive immunotherapy in renal adenocarcinoma.

Dr. Stutman's research is focused in two areas: (1) the ontogeny, maintenance and involution of functional T cells, including T cell subsets and the role of the thy-

mus proper in such processes, and (2) the immunological components of the tumor-host interaction, especially the production of cytotoxic effector cells which can kill tumor cells by production of tumor necrosis factor (TNF) and other lytic molecules.

Dr. Weksler's research concerns two areas: (1) The biology of autoreactive T lymphocytes and (2) the immunobiology of aging. The former studies are aimed at understanding the development and regulation of the immune system; the latter at understanding the biological processes that lead to the diseases of aging.

Dr. Yang's laboratory is conducting studies of the molecular mechanisms controlling class I MHC gene expression during cellular differentiation and neoplastic transformation, as well as the biological role of class I MHC determinants in tissue transplantation. Another area of study is the activation and differentiation of T-lymphocytes and characterization of T-lymphocyte differentiation antigens and their function.

Recent Publications

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Molecular Biology

Faculty

Dennis G. Ballinger
Francis Barany
Kenneth I. Berns
Peter Besmer
Anthony M. C. Brown
Moses V. Chao
Robert DeLotto
Dale Dorsett
Erik Falck-Pedersen
Eli Gilboa
Neil R. Hackett
William S. Hayward
William K. Holloman
Jerard Hurwitz
Joseph R. Jack
Elizabeth Lacy
Monika Lusky
Arthur J. Lustig
Kenneth J. Marians
Norma Neff
Michael E. O'Donnell
Mary Ann Osley
Samuel D. Rabkin
Jeffery V. Ravetch
Michael B. Sheffery
Stewart Shuman
Paul Tempst
Paula Traktman

Research Activities

The faculty of the Graduate Program in Molecular Biology offers graduate research training in a variety of systems on problems related to the replication, transcription, translation and function of genetic information in developing organisms and differentiating cells. The research activities of the faculty can be divided into four broad areas of study: DNA replication and recombination; regulation of RNA synthesis and processing; receptors and their role in cell function and differentiation; and retroviruses, proto-oncogenes, and development.

DNA Replication and Recombination

DNA replication in prokaryotes is under study in the laboratories of *Dr. Marians* and *Dr. O'Donnell. Dr. Marians* focuses on studies of the enzymological mechanisms of DNA replication in *Escherichia coli,* using cell-free systems. The use of *in vitro* DNA replication systems composed of purified replication proteins enables detailed analyses of the interaction of the replication proteins with each other and with the DNA template. The role of topology in DNA replication, as well as the mechanisms of DNA topoisomerases, is also under study in his lab. A detailed examination of the molecular mechanics of DNA replication is also the focus of *Dr. O'Donnell*'s laboratory. The dynamic motions on templates of the multi-protein replicative polymerase of *E. coli* and its interaction with other proteins at the replication fork are under study. *Dr. O'Donnell* is also beginning to investigate the control of initiation of replication of Epstein-Barr virus.

Faculty investigating eukaryotic DNA replication employ several different viral systems. *Dr. Berns* uses the life cycle of the human adeno-associated virus AAV2 to model how gene expression and DNA replication are regulated. *Dr. Hurwitz*'s labora-

tory uses the adeno and SV40 viral DNA replication systems as probes for the enzymatic mechanisms of cellular DNA replication. The regulation of bovine papilloma virus DNA replication is studied by *Dr. Lusky* using molecular genetics to define and characterize the viral genes required for replication *in vivo* and using biochemical approaches to study BPV DNA replication *in vitro*. The replication of AAV, adenovirus, SV40, and BPV require host cellular proteins, thus these viral systems also allow these investigators to study the endogenous mechanisms for DNA replication in mammalian cells.

Both *Dr. Traktman*'s and *Dr. Rabkin*'s laboratory study the replication of large DNA viruses that encode their own DNA replication machinery. *Dr. Traktman* employs both biochemical and molecular genetical techniques to define the genes of vaccinia virus that are required for its replication. *Dr. Rabkin* is developing an *in vitro* system for the replication of herpes simplex viral DNA in order to identify and characterize the proteins involved in these processes.

The molecular processes controlling the structure, function, and genetic properties of chromosomes are being studied by the laboratories of *Drs. Lustig* and *Hackett*. Using molecular genetics and biochemistry, *Dr. Lustig* is investigating the mechanisms that have evolved for replicating telomeres, the unique ends of chromosomes required for stability, and the role these sequences play in chromosome segregation and recombination.

Dr. Hackett is also interested in the structure of the bacterial genome and how it changes over time. His immediate objective is to construct detailed restriction maps of the genomes of several related isolates of *Halobacterium halobium*. Comparisons will reveal how genome structure evolves both normally and in response to selective pressure.

Another key cellular process that occurs on DNA is the exchange of genetic information through the process of recombination. *Dr. Holloman*'s laboratory studies the genes and the enzymes involved in this complicated process. Model studies focus on the mechanism of synapsis and DNA strand exchange.

Regulation of RNA Synthesis and Processing

Many aspects of the regulation of gene transcription and RNA processing are under active investigation by members of the Molecular Biology Program. These include the definition of controlling DNA and RNA sequences, the identification and characterization of the proteins and enzymes involved, and the elucidation of the mechanisms that dictate temporal and spatial patterns of gene expression.

Using genetic and molecular genetic techniques, *Dr. Osley* is investigating the basis of the periodic expression of the histone genes in yeast.

Research in *Dr. Sheffery*'s laboratory is directed at understanding how proteins and DNA interact to form structures that influence gene transcription, using the mouse globin genes as a model. Particular effort is devoted to understanding tissue-specific gene expression.

In a related effort, the basis of sequence-specific recognition of DNA by proteins is studied by *Dr. Barany* using a combination of molecular biology, X-ray crystallography, and NMR spectroscopy.

Dr. Falck-Pedersen is characterizing the regulatory elements involved in eukaryotic transcription termination and RNA processing using genetically reconstructed adeno-virus as a model vector. Both biochemical and genetic aspects of transcrip-

tional control, with particular emphasis on transcription termination in purified *in vitro* systems, are under study by *Dr. Shuman* using vaccinia virus as a model.

Dr. Dorsett's laboratory is using both genetic and molecular genetic techniques to define the *cis*- and *trans*-acting factors that regulate virus-like transposons in *Drosophila.* These transposons are responsible for a number of naturally occurring mutations in *Drosophila* and have been shown to affect the expression of the mutated host genes at the level of transcription.

Dr. Hurwitz's group studies the enzymes and enzymological processes involved in mRNA splicing in human cells.

Receptors and Their Role in Cell Function and Differentiation

Several laboratories are investigating receptors that transmit signals to the interior of the cell after forming a complex with a specific ligand.

In a series of experiments in *Dr. Ravetch*'s laboratory, the molecular genetic analysis of cell surface receptor proteins is being conducted, aimed at defining their modulation, mechanism of signal transduction, and developmental regulation by isolation and characterization of genes that code for proteins binding immunoglobulins (FC receptors), by studying the interaction of the malaria producing parasite with the erythrocyte, and by characterizing the activated macrophage phenotype.

Dr. Neff is interested in the role of vacuolar-type proton ATPases in endocytosis and vacular functions in *Saccharomyces cerevisiae.* Toward this goal two genes have been cloned that have identity with proton ATPase subunits, one of which codes for a proton channel protein.

The gene for human nerve growth factor receptor has been isolated by *Dr. Chao*'s laboratory. Recombinant DNA technology is being used to study the important structural features of the gene, the molecular basis of differential receptor expression during development, and the mechanism of signal transduction.

Using the generation of transgenic mice as the major experimental tool, *Dr. Lacy* is studying the regulation and function of the CD4 and CD8 cell surface glycoproteins during T-cell maturation in the thymus. CD4 and CD8, respectively, recognize and bind to nonpolymorphic regions on class II and class I major histocompatibility complex (MHC) proteins; their interactions with the MHC proteins are believed to regulate the signals transduced by the T-cell receptor during T-cell development.

Retroviruses, Proto-oncogenes, and Development

The research activities of the Molecular Biology faculty in this area are quite diverse and include studies on retroviral vectors, retroviral induced neoplastic diseases, the role of proto-oncogenes in cell and tissue differentiation, embryonic axis formation and the development of the nervous system in *Drosophila,* and gene function in the early mouse embryo.

Efficient methods to introduce genes into human cells, using retroviruses, are being developed in *Dr. Gilboa*'s laboratory. These methods are used to develop an efficient gene therapy protocol for the treatment of genetic disorders and to modify and amplify specific immune responses in the human patient.

The major objective of *Dr. Hayward*'s laboratory is the elucidation of the molecular basis of the induction of neoplastic disease, using avian leukosis viruses as model systems. Of particular interest at the present time is the identification and characteri-

zation of oncogenes involved in late stages of tumor progression.

The current research goal in *Dr. Besmer*'s laboratory is to understand the function of the proto-oncogene c-*kit,* a transmembrane receptor kinase; the c-*kit* ligand is being sought and molecular aspects of c-*kit* mediated signal transmission are being investigated in hemotopoietic cell differentiation and development.

Dr. Brown is studying molecular mechanisms of oncogene action, concentrating on tumors induced by the mouse mammary tumor virus (MMTV). A major focus of his research is the function of the proto-oncogene *int*-1, which is activated by MMTV in mammary tumors and is also implicated in early embryonic development of the nervous system.

Dr. Tempst's laboratory studies the regulation, processing and activities of antibacterial peptides, which are major components of the insect immune system. High resolution 2D gel electrophoresis and high sensitivity sequencing techniques are being developed to investigate cellular events at the single protein level.

Drs. DeLotto, Jack, and Ballinger use *Drosophila* as an experimental organism for the study of development and cell determination. *Dr. DeLotto* studies the biochemical mechanisms underlying embryonic axis formation using genetic and molecular biological approaches. *Dr. Jack* is currently investigating the molecular genetics of development of the peripheral nervous system. *Dr. Ballinger*'s laboratory is investigating mechanisms of differentiation, pattern formation and behavior in the *Drosophila* visual system with a combination of molecular and genetic techniques. Photoreceptor neurons are the subject of studies focused on a terminal differentiation antigen, and on the mechanism of pattern formation. To investigate the function of complex neural processing networks, behavioral mutations that alter the processing of visual information are under study.

Dr. Lacy's group is working on identifying and isolating genes that are required for early mouse development by generating insertional mutations in the germ line of transgenic mice.

Recent Publications

Ballinger, D. G. (with Benzer, S.), *Photophobe (Ppb),* a *Drosophila* mutant with a reversed sign of phototaxis; the mutation shows an allele-specific interaction with *sevenless. Proc. Natl. Acad. Sci. U.S.A.* 85:3960–3964, 1988.

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Neuroscience

Faculty

Harriet D. Baker
Dennis G. Ballinger
Ronald G. Blasberg
Dana H. Bovbjerg
Michael Caudy
Arthur J. L. Cooper
Robert B. Darnell
Henry M. Furneaux
Daniel Gardner
James G. Gibbs
Gary E. Gibson
Steven A. Goldman
Bernice Grafstein
Charles E. Inturrisi
Tong H. Joh
Mary P. Meeley
Teresa A. Milner
Michiko Okamoto
Gavril W. Pasternak
Carol K. Petito
Virginia M. Pickel
Fred Plum
Jerome B. Posner
William A. Pulsinelli
Donald J. Reis
David A. Ruggiero
Jeri A. Sechzer
Gerard P. Smith
Peter E. Stokes
Ellen Townes-Anderson
Jonathan D. Victor
Bruce T. Volpe
Claes R. Wahlestedt

Research Activities

Dr. Baker studies the factors underlying the determination and maintenance of neuronal phenotype. Using the olfactory system as a model, Dr. Baker focuses her research on neurotransmitter expression during development and aging as well as in response to deafferenting lesions. Immunocytochemical, neurochemical, *in situ* hybridization, molecular biological and neuronal tracing techniques are utilized in these studies.

Dr. Ballinger's research interests include molecular and genetic studies of the development and function of the *Drosophila* visual system.

Dr. Blasberg's research projects include *in vivo* imaging studies in both small animals (quantitative autoradiography; QAR) and human subjects (positron emission tomography; PET) related to: 1) brain and brain tumor physiology (iododeoxyuridine incorporation in DNA, glucose metabolism, blood flow and transcapillary transport); 2) opiate receptor imaging using specific radiolabeled opiate antagonists under normal and altered states; and 3) correlation between the physiological response and brain concentrations of different radiolabeled opioid analgesics following i.v. administration.

Dr. Bovbjerg studies the interactions between the brain and the immune system. His particular interest is classically conditioned changes in immune function. Research techniques include a variety of *in vitro* and *in vivo* assessments of immune function. Other research interests include "stress" effects on immune function and behavioral effects of immunologic manipulation.

Dr. Caudy is interested in the molecular-genetic mechanisms which control neuronal pattern formation during development. He is studying a network of cell determination genes which control the switch between neuronal and non-neuronal cell fates in *Drosophila* embryos. These genes encode a family of DNA-binding transcription factors ("helix-loop-helix" proteins) whose human homologues are proto-oncogenes.

Dr. Cooper's research interests include α-Keto acid chemistry and biochemistry; pyridoxal 5′-phosphate enzymes; investigations of enzyme mechanisms; design of enzyme inhibitors as drugs; amino acid and ammonia metabolism in normal and disease states; cerebral energy metabolism (with particular emphasis on the malate-aspartate shuttle)and its disruption in various disease states; design and use of molecules labeled with short-lived radioisotopes for positron emission tomography of the human tissues and for tracer studies in animals; neurochemical consequences of cerebral ischemia; molecular biology of glutamine transaminase K/cysteine *S*-conjugate β-lyase, ω-amidase in rat kidney; mitochondrial defects in Alzheimer's disease.

Dr. Darnell is working on the cloning and characterization of onconeural genes, which are defined by the paraneoplastic neuronal syndromes. These genes are coordinately expressed in discrete populations of neurons and tumor cells, and can be readily cloned using autoantibodies from affected patients. Onconeural genes are of interest both as a tool for analyzing neuron specific development and function, and as a means for contrasting the function and regulation of gene expression in neurons and tumors.

Dr. Furneaux's laboratory identifies gene products that regulate the development of the neuronal phenotype. The focus of these studies is a unique group of anitgens which are exclusively expressed in neurons and are recognized by the sera of patients with paraneoplastic neurological syndromes, rare disorders in which an anti-tumor immune response is thought to be misdirected against the brain. A number of these antigens have been cloned and characterized. One (HuD) is a neuronal-specific RNA binding protein and is highly homologous to a *Drosophila* protein (Elav) which controls neuronal cell fate. Another (CD3) is expressed in a subset of mammalian neurons and has features that suggest it functions in the control of neuronal gene expression. Since these antigens are also uniquely expressed in human systematic tumors, these recombinant proteins provide important reagents for diagnosis and therapy.

Dr. Gardner studies how neurons use chemical synaptic transmission to communicate with one another. Neurons in ganglia of the mollusc *Aplysia* are probed by intracellular recording, voltage clamping, patch clamping, and computer-based analysis to yield principles of organization of cell networks. One project focuses on properties of transmitter-activated channels which are altered to produce different postsynaptic currents. A second project combines neurophysiology with artificial intelligence techniques to ask how neuronal biophysics coordinates the activity of neurons in a network.

Dr. Gibbs' research focuses on the neurobiology of motivated behaviors, especially the neuroendocrine mechanisms controlling feeding behavior in animals and the pathophysiology of eating disorders in humans.

Dr. Gibson examines the relation of signal transduction systems (e.g. calcium, PI cascade and cyclic AMP) to oxidative metabolism, neurotransmitters, altered brain function and cell death. He is also examining the mechanisms by which alterations in second messengers regulate gene expression, including the catecholamine enzyme

genes. These interactions are examined in animal models of conditions that alter memory and other mental functions in man (aging, hypoxia/ischemia and thiamin deficiency) as well as in tissues from Alzheimer patients. *In vivo* neurotransmitter metabolism and calcium homeostasis are related to behavior. *In vitro* systems are utilized to examine molecular mechanisms. Human studies include measurements on autopsied brain as well as studies of calcium dynamics in lymphocytes, red blood cells and cultured skin fibroblasts.

Dr. Goldman is interested in neuroplasticity in the adult brain. His research is focused upon the molecular mechanisms subserving neural production, migration and differentiation in a neurogenic region of the adult songbird brain. These cellular events are examined both *in vivo* and *in vitro,* with the aim of determining the regulatory constraints on neurogenesis and neuroblastic migration in the adult CNS.

Dr. Grafstein is concerned with problems of nerve regeneration and the response of nerve cells to injury. Techniques used include light and electron microscopy and radioactive isotope methods for analyzing the axonal transport of proteins and other cellular constituents.

Dr. Inturrisi studies the factors that regulate endogenous opioid peptide biosynthesis and release and the behavioral consequences of alterations in this system. Molecular probes for opioid peptide mRNAs are used to examine neurogenic and hormonal control of gene expression using *in vivo* and *in vitro* models.

Dr. Joh's main interest is to study the gene expression and regulation of neurotransmitter enzymes, receptors and neuron specific proteins. Multidisciplinary studies with molecular biologists, developmental biologists, neurobiologists and histochemists include structure/function analyses of genes coding for these neuronal elements, characterization of molecular events occurring during neuronal degeneration, and investigation of transgenic mouse models of genetically altered neurotransmission.

Dr. Meeley is interested in neurochemical regulation of synaptic transmission. The model system currently studied is brainstem pathways controlling arterial pressure and heart rate. The focus is on elucidation of specific transmitters involved in mediating autonomic signals within principle nuclei, and their possible interactions, and on isolating and identifying new putative transmitters, e.g. a clonidine-like substance in the brain, the putative endogenous ligand interacting with imidazole receptors in the ventrolateral brainstem. Methods of purification of small molecules and specific assay systems are developed.

Dr. Milner studies the ultrastructural basis for transmitter interactions in (1) the septo-hippocampal pathway involved in learning and memory; and (2) brainstem and spinal cord nuclei associated with cardiovascular regulation. Both studies utilize either dual labeling immunocytochemical techniques or immunocytochemical methods combined with tract-tracing techniques at the electron microscopic level of analysis. The major transmitters of interest include catecholamines, acetylcholine, opioids, and somatostatin.

Dr. Okamoto researches neuropharmacologic bases of the drug dependence produced by centrally acting drugs in adults and neonates exposed to drugs during their fetal period. Central nervous depressant drugs, i.e. alcohol, barbiturates and benzodiazapines have been her major interest. Electrophysiologic, neurochemical and behavioral effects are studied during acute and chronic drug treatment: functional and cellular mechanisms for the tolerance and dependence production are investigated: chronic effects of these drugs are studied on developing synapses and on the maturation of the nervous system.

Dr. Pasternak examines the molecular pharmacology of centrally active analgesics. Work in the laboratory currently is focused upon the biochemical and pharmacological characterization of the various opiate receptor subtypes. One goal of the laboratory includes examining membrane-bound and affinity-purified receptors and their potential coupling with effector systems. Another is the correlation of the various subtypes with specific opiate actions *in vivo.* Finally, the anatomical localization of these sites within the central nervous system is studied with quantitative autoradiography. Many of these approaches have utilized a series of opiate affinity labels developed within the laboratory.

Dr. Petito studies neuronal-glial interactions following experimental cerebral ischemia, using immunohistochemistry, electron microscopy and *in situ* hybridization techniques. A second major research interest concerns the pathogenesis of CNS damage due to HIV infection and using similar methodologies.

Dr. Pickel's current and projected research uses immunocytochemical and molecular probes to examine the cellular substrates involved in (1) *automatic regulation* and fluid homeostasis, (2) normal and abnormal *movement,* and (3) the *rewarding properties of opiates* and other drugs of abuse. Emphasis is on studying interactions between central catecholaminergic (noradrenergic, adrenergic and dopaminergic) neurons and neurons containing other putative transmitters such as acetylcholine, GABA, and opioid or other endogenous peptides.

Dr. Plum, Chairman of the Department of Neurology and Neuroscience, focuses his research efforts on cerebral metabolism in disease states and the identification of cellular-subcellular mechanisms responsible for ischemic cell death.

Dr. Posner is interested in the identification and characterization of "onconeural" antigens shared by the central nervous system and certain tumors and identified by antibodies in the serum of patients with neurological paraneoplastic disorders.

Dr. Pulsinelli studies the cellular and molecular mechanisms of ischemic injury to brain neurons and glia. Techniques used in these studies include *in vivo* and *in vitro* (tissue culture) models of ischemic injury to brain cells, radioisotopic measurements of cerebral blood flow and glucose metabolism, fluorometric measurements of high energy organic metabolites, analysis of phosphorylation of brain proteins, and light and electron microscopic studies of cell injury.

Dr. Reis' research interests are the central neural and neurochemical mechanisms governing control of the autonomic nervous system, cerebral blood flow and metabolism. His research also includes mechanisms governing the death of brain neurons in response to aging and injury.

Dr. Ruggiero investigates anatomical and neurochemical pathways in brain which maintain normal resting levels of arterial blood pressure; neural substrates of the baroreceptor reflex; pathways underlying the cerebellar regulation of autonomic activities and cerebral blood flow; areas of autonomic representation in cerebral cortex and brainstem reticular formation; adrenaline synthesizing neurons, their pathways in the central nervous system; their role in cardiopulmonary regulation; and afferent (pain) neurotransmission.

Dr. Sechzer's research interests include early development, behavioral toxicology, neural mechanisms of memory and learning, and neurosensory perception. Her current activities include: (1) The effect of lithium chloride on maternal behavior and early development; (2) Olfactory and gustatory perception in depression; (3) Bioethical issues concerning the use of animals in research and education.

Dr. Smith focuses on the behavioral neuroscience of eating and its disorders. Current experiments include the measurement of central monoamines during eating behavior, the role of gut peptides, such as cholecystokinin, to stop eating, animal models of eating disorders using genetic and sham feeding rats, and the experimental analysis of taste and eating in human patients with various types of eating disorders.

Dr. Stokes is interested in neuroendocrine function in affective disease. Measurements of hypothalamic-pituitary-adrenocortical (HPA) function at various levels of this axis are obtained in patients with depression vs. healthy normal controls and patients with other psychiatric diagnoses. Current specific interests include: response of the HPA system to administration of CRF, ACTH, dexamethasone and adrenocortical steroid blockers, pharmacokinetics of dexamethasone, measurement of multiple adrenal steroids, investigation of the relationship between HPA function and biogenic amine and sympathetic nervous system activity. A second area of interest is the investigation of lithium pharmacokinetics and the pharmacology-toxicology of lithium isotopes in animals and humans.

Dr. Townes-Anderson examines the cell biology of retinal neurons. Currently, cells isolated from the adult vertebrate retina are used *in vitro* to address questions concerning synaptic function and plasticity. Membrane recycling at the photoreceptor synapse is being examined with morphological techniques including rapid freezing and electron microscopy. Localization of neurotransmitter receptors is performed on isolated second and third order neurons. And regeneration of functional synapses is being investigated in cultures of adult nerve cells.

Dr. Victor studies visual processing at retinal and cortical levels. Research techniques include single-unit recording, evoked potentials, psychophysics, and mathematical modeling. Other research interests include novel approaches to nonlinear systems analysis and signal processing as applied to neural systems.

Dr. Volpe investigates the neuroanatomy and functional outcome in animal models of selective neuronal injury and aging. Techniques used include immunohistochemistry, *in situ* hybridization, instrumental and classical conditioning.

Dr. Wagner's laboratory focuses on the application of biochemistry, genetics and molecular biology to understanding the effects of peptide growth factors and other signaling molecules during normal and pathological neural development as well as in response to injury.

Dr. Wahlestedt's interests center on neurotransmission and associated intracellular signal transduction. Research projects include (1) molecular cloning of neurotransmitter receptors; (2) characterization of a novel cellular pathway involved in Ca^{2+} signaling; and (3) effects of psychostimulants on brain neuropeptide stems. Clinical collaborations concern hypertension and affective disorders.

Recent Publications

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Pharmacology

Faculty

Joseph R. Bertino
Walter W. Y. Chan
Ting-Chao Chou
Diane Felsen
Owen W. Griffith
Steven S. Gross
Lorraine J. Gudas
Charles E. Inturrisi
Roberto Levi
John Mendelsohn
Michiko Okamoto
Gavril W. Pasternak
Hans J. Prochaska
Marcus M. Reidenberg
Arleen B. Rifkind
Walter F. Riker, Jr. (Emeritus)
Paul D. Roepe
David A. Scheinberg
Kathleen W. Scotto
Francis M. Sirotnak
Hazel H. Szeto
Kyoichi A. Watanabe

Research Activities

Dr. Bertino is interested in the transfer of drug resistant genes into hematopoietic cells: Both electroporation and viral vectors have been studied as methods of introducing drug resistant genes into mammalian cells in culture, and into bone marrow cells. The aim is to produce long-term expression of drug resistant genes in hematopoietic stem cells. Both *in vitro* (CFU_c) and *in vivo* (CFU_s) studies are being pursued in mice. The purpose of these studies is to produce drug resistance of marrow stem cells, thus allowing larger doses of the desired drug to be utilized for therapy.

Site specific mutagenesis of the dihydrofolate reductase gene: The purpose of these studies is to better understand the effects of specific amino acid substitutions on substrate and inhibitor binding, and to develop an altered enzyme with a decreased affinity for methotrexate, but with good catalytic activity for gene transfer studies.

Mechanisms of natural and acquired resistance to folate antagonists and fluoropyrimidines: Human tumor cell lines and fresh human tumor samples (sarcoma, leukemia, colon cancer) are studied to determine mechanisms of resistance to these drugs. Sensitive assays to determine the molecular basis of drug resistance, including gene amplification, gene mutations, and transport and/or defects in drug catabolism have been developed.

Dr. Chan is interested in the functions and interactions of prostaglandins and neurohypophysial peptides in the kidney and the uterus. Current research covers investigative studies from subcellular levels to the whole organism. Certain analogs of oxytocin and vasopressin have been found to stimulate urinary sodium and water excretion. This renal effect of the peptide appears to be mediated by renal prostaglandin release. The biochemical mechanisms of this peptide-induced prostaglandin release is the principal concern of our research. Also studied are the renal activities of peptide analogs specifically synthesized for the project with the aim to discover specific prostaglandin-releasing and/or anti-vasopressin (anti-ADH) peptides that may be useful for the treatment of renal hypertension.

In the uterus, the roles of prostaglandins and oxytocin in the regulation of uterine contractions and termination of pregnancy are investigated. This research seeks an understanding of the mechanism of initiation of labor, especially relating to preterm labor. Oxytocin-receptor and gap-junction formations in myometrial cells are important biochemical and morphological markers in the initiation of labor. Accordingly, a study is made of the effects of prostaglandins and oxytocin on the density of oxytocin-receptors and on the formation of gap-junctions in myometrial cells. Highly potent oxytocin antagonists have been synthesized for this project and their application in the prevention of preterm labor in the pregnant rat model will be investigated. Also studied are the physiological roles of ovarian oxytocin and uterine prostaglandins in the function of the corpus luteum, as well as the potential of intervention of this ovarian-utero axis in the regulation of fertility or as causal factor in abortion.

Dr. Chou's research activity includes three areas: 1) Developmental therapeutics of new antitumor and antiviral agents using synthetic compounds and plant products; 2) Biochemical studies on selected compounds at molecular level with the aims of elucidating mechanism of action, selectivity of effect or the development of drug resistance and cross-resistance, and 3) Theoretical biology of deriving generalized equations based on the principle of mass-action law for dose-effect analysis, receptor topological analysis, and the quantitation of multiple drug interactions in terms of synergism and antagonism. In the first area, we have recently conducted preclinical pharmacological studies on acridone alkaloids such as glyfoline as an anticancer agent and on 3′-fluoro-3′-deoxythymidine (FLT) as anti-AIDS agent. The latter has entered clinical trials. In the second area, we have studied DNA intercalators, such as chrysophanol and acridine derivatives, as inhibitors of DNA topoisomerase type II. We examined topoisomerase II mediated-drug induced DNA cleavages and the inhibition of topoisomerase by measuring the relaxation of supercoiled DNA, decatenation of kinetoplast DNA and the stabilization of cleavable complex. Monofunctional and/or bifunctional chloroethyl alkylating groups have been added to some of these compounds for active site and binding site studies. In the third area, the median-effect equation and the multiple drug-effect equation for isobologram and FA-CI plot have been derived and computer software for IBM-pc and Apple microcomputers have been developed for automated data analysis. The method has been applied in various drug combination studies for anticancer agents, antiviral agents (anti-HIV, anti-HSV, etc.) and for immunosuppressants in organ transplantation.

Dr. Felsen is interested in the role of arachidonic acid metabolites (AAMs; prostaglandins, leukotrienes and hydroxy acids) and other mediators of inflammation (e.g., cytokines, including tumor necrosis factor and interleukins, and platelet-activating factor) in renal and urinary tract function. The role of these compounds both *in vivo* and *in vitro* is studied using a variety of techniques. In obstructive uropathy, renal function is assessed through measurements of renal blood flow, glomerular filtration rate, sodium, potassium and water excretion and other parameters. *In vitro,* cell culture and molecular biological techniques are used to assess renal mediator synthesis. Likewise, samples of patients with interstitial cystitis (a chronic bladder disease) are examined for inflammatory mediators in an attempt to both better define this disease and to uncover new treatments for it.

Dr. Griffith's research involves the design, synthesis and utilization *in vivo* of enzyme selective inhibitors and substrates. These compounds are used both to evaluate and to control the metabolite flux through various pathways in intact animals. Recent studies have focused on the manipulation of glutathione and cysteine metabolism.

Enzyme-selective inhibitors were developed that allow both glutathione biosynthesis and utilization to be blocked; techniques allowing extracellular cystine formation to be controlled were also developed. The inhibitors were shown to be useful in treating animal trypanosomiasis, enhancing oxidative killing of tumor cells, and preventing the formation of leukotriene C. In other studies, novel carnitine analogs were synthesized as inhibitors of carnitine palmitoyltransferase and were shown to block long-chain fatty acid oxidation *in vivo.* In mice with diabetes, a disorder characterized by underutilization of glucose and overutilization of fats, these compounds prevent ketoacidosis and restore normal blood glucose levels. Studies are continuing in which carnitine analogs are used to probe the regulatory interactions between carbohydrate and fatty acid metabolism. Studies of nitric oxide synthesis have been initiated in collaboration with *Drs. Levi* and *Gross.*

Dr. Gross' research focuses on nitric oxide, a newly discovered signalling molecule whose function is just beginning to be elucidated. Principal among the known actions of nitric oxide is its key role in vascular homeostasis and blood pressure regulation, mediation of cytotoxic and cytostatic effects of certain cells of the immune system and function as a chemical transmitter/second messenger in the brain. Deficient production of nitric oxide (also known as endothelium-derived relaxing factor; EDRF) by the vascular endothelium has been implicated in hypertension, atherosclerosis and diabetes. On the other hand, overproduction of nitric oxide may be responsible for the hypotension which occurs during bacterial sepsis and in response to the chemotherapeutic use of cytokines. The emphasis of *Dr. Gross'* research is to reveal biochemical mechanism(s) of nitric oxide synthesis, regulation and actions in physiology and disease.

Dr. Gudas' laboratory has several long-term research aims. One major goal is to learn about the regulation of gene expression during mammalian cell differentiation, while another is to understand the mechanism by which vitamin A and its derivatives (retinoids) control both cellular differentiation and cellular proliferation. Retinoids exert effects on cell differentiation, pattern formation in development, limb regeneration, and the inhibition of the process of tumor formation. As a model differentiation system, the retinoic acid induced differentiation of murine teratocarcinoma stem cells is being studied; these stem cells are similar in many respects to the pluripotent inner cell mass cells of the mouse blastocyst. The teratocarcinoma stem cells differentiate into an epithelial cell type called parietal endoderm when they are treated with retinoic acid. A number of genes which are expressed at different times during this differentiation process have been cloned. Currently the structures of these genes is being determined, including the sequences of their promoters, in order to understand how their expression is regulated during differentiation. The actions of the nuclear receptors for retinoic acid, retinoic acid receptors α, β and γ, are being elucidated, as is the mechanism by which cyclic AMP can enhance the action of retinoids in this system. Finally, since the teratocarcinoma stem cells resemble pluripotent cells of the early mouse embryo, the expression of the teratocarcinoma differentiation related genes in early mouse embryos and in early *Xenopus* embryos are being analyzed.

Dr. Inturrisi's research activities are directed toward understanding the biochemical basis of the pharmacodynamic effects of opioids. In laboratory animals studies utilizing molecular probes are aimed at defining the factors that regulate opioid peptide gene expression, biosynthesis and release so as to establish the relationships between treatments that alter opioid peptides and their mRNAs and the functions (e.g., analgesia) of the endogenous opioid peptides. Clinical studies are aimed at de-

veloping pharmacokinetic-pharmacodynamic models from patient data that can be used to improve analgesic therapy and provide insight into the quantitative aspects of the development of tolerance to opioids in these patients. The ultimate goal of these studies is a more precise definition of the interrelationship between the exogenous and endogenous pain modulating systems.

Immune hypersensitivity reactions are often associated with severe cardiovascular dysfunction. The long-term goal of *Dr. Levi*'s research has been to provide an understanding of the immunopharmacologic mechanisms responsible for the epidemiologically demonstrated association between IgE serum levels and cardiovascular disease.

His laboratory is presently characterizing a recently discovered endothelial dysfunction. Following immediate hypersensitivity reactions, arteries become grossly defective in their response to endothelium-dependent vasodilators and hyperresponsive to vasoconstrictors. The laboratory is therefore assessing the involvement of endothelium-derived relaxing factor (EDRF) (identified as nitric oxide, NO) in these reactions in various vessels, coronary included.

Histamine, released by many common non-immunologic stimuli and in myocardial ischemia, is predominantly a vasodilator, but becomes a potent local constrictor at coronary vessel sites affected by atherosclerosis. New pharmacologic tools are now available to assess the biology of EDRF/NO; e.g., L-N -methylarginine. Thus the laboratory is determining EDRF release from the heart, its contribution to histamine's effects on the coronary vessels, and the conditions and agents which may modulate the production, lifetime and vasodilating potency of histamine-released EDRF. Because histamine is released in myocardial ischemia, it is conceivable that dysfunctions of the EDRF system could precipitate histamine-induced coronary spasm leading to myocardial infarction, arrhythmias and sudden cardiac death.

Dr. Mendelsohn's laboratory is studying the epidermal growth factor (EGF) receptor from a number of points of view. (1) Exogenous and endogenous agents that control autophosphorylation of the EGF receptor are being investigated. These include EGF and TGF-α, as well as regulators of protein kinase C, activated receptors for other growth factors, and phosphatases. (2) The interactions between endogenous growth factors (autocrine loops) and other agents that promote or inhibit cell proliferation, including TGF-β and the interferons are being explored. (3) The laboratory has produced anti-EGF receptor monoclonal antibodies that inhibit EGF and TGF-α binding and block receptor activation. These are utilized in the above biologic experiments, and preclinical studies and clinical trials in patients are being carried out, exploring the capacity of antireceptor antibodies to act as antitumor agents. Conjugates of antireceptor antibodies with cytotoxic agents and radionuclides are under investigation in human tumor xenograft model systems.

Dr. Okamoto studies the neuropharmacologic bases of the drug dependence produced by centrally acting drugs in adults and neonates exposed to drugs during their fetal period. Central nervous depressant drugs, i.e. alcohol, barbiturates and benzodiazepines have been her major interest.

Electrophysiologic, neurochemical and behavioral effects are studied during acute and chronic drug treatment: functional and cellular mechanisms for the tolerance and dependence production are investigated: chronic effects of these drugs are studied on developing synapses and on the maturation of the nervous system.

Dr. Pasternak studies the biochemical and pharmacological properties of various subclasses of opiate receptors within the central nervous system. Molecular ap-

proaches include binding studies and affinity labeling of receptors using a series of irreversible opiate agonists and antagonists developed and synthesized in this laboratory. Computerized quantitative autoradiographic studies are aimed at the distribution of the various subtypes of receptors, complementing the biochemical studies. In addition to these molecular studies, the biochemically defined binding subtypes are correlated with specific opiate actions, including analgesia, respiratory depression, gastrointestinal motility and hormone modulation, using classical pharmacological techniques. Again, the selective affinity labels developed in this laboratory have proven invaluable in these studies.

Dr. Prochaska's major research interests are geared toward the design of pharmacological strategies for preventing cancer in man. It is well recognized that many compounds are capable of blocking the toxic and neoplastic effects of carcinogens; moreover, these compounds and their naturally-occurring congeners may play an important role in the relationship of diet to cancer. Many diverse anticarcinogens induce Phase II enzymes and such an induction is now accepted to be a major mechanism for cancer prevention. The laboratory will try to better elucidate the molecular mechanisms for Phase II enzyme induction so that more potent and non-toxic compounds can be designed. An additional goal is to develop animal models that reflect human populations which are particularly prone to develop malignancy so that the validity of cancer chemoprevention in man can be demonstrated.

Dr. Reidenberg pursues a fundamental question in clinical pharmacology, "Why do different people react differently to the same dose of the same medicine?" His program in clinical pharmacology addresses this question in several different ways. Currently, he is studying the clinical pharmacology of gossypol and other bioflavinoids. This is related to development of gossypol as a male oral contraceptive and the problem of hypokalemia in some men taking this drug. A clinical trial of high dose gossypol currently going on to study the clinical pharmacology of it in patients with advanced cancer has produced a response in 3 of 16 evaluable patients. Studies of gossypol actions and studies relating gossypol levels to effects in both cancer patients and men desiring contraceptive therapy are also ongoing.

The other area of interest, drugs in the elderly, is currently being pursued by studies of the clinical pharmacology of mitochondria. These studies include *in vitro* studies of isolated mitochondria as well as studies in patients.

Dr. Rifkind's interest in environmental toxicology has led to the investigation of the biochemical mechanisms of polychlorinated biphenyl (PCB) and dioxin toxicity. These compounds bind to a cytosolic receptor (*Ah* receptor) which controls the expression of a group of gene products including specific isozymes of cytochrome P-450. Dr. Rifkind's laboratory is studying the relationship of cytochrome P-450 to the diverse toxic manifestations of PCB and dioxins. These include weight loss, thymic involution, tumor promotion, and cardiac toxicity. Her laboratory recently discovered that the cytochrome P-450 induced by toxic PCBs and dioxins increases the metabolism of the endogenous membrane fatty acid, arachidonic acid, to epoxides and monohydroxylated products. These arachidonic acid metabolites have biologic activities consistent with involvement in PCB and dioxin toxicity. Current studies focus on (1) the role of arachidonic acid metabolism in PCB and dioxin toxicity and (2) the effects of dioxin induced changes in arachidonic acid metabolism on signal transduction pathways in heart and liver.

Dr. Roepe's research is focused on obtaining a molecular-level understanding of the structure and function of adenosine triphosphate (ATP)—coupled active trans-

port systems, particularly multidrug efflux pumps (MDR proteins) and their relatives. A promising new biophysical technique developed in recent years for the study of biological membranes and membrane proteins is Fourier transform infared (FTIR) spectroscopy. FTIR studies of light-activated membrane proteins during the past several years have demonstrated that high quality dynamic information at the single bond level is attainable for membrane protein-mediated enzymatic processes. It is therefore possible to delineate key molecular events, including those at the single bond level, in other membrane proteins and receptors. A key drawback to these studies is the inability to isolate large quantities to membrane proteins in a form amenable to spectroscopy (i.e. substantially delipidated yet functional). Thus, another major activity of our laboratory is the investigation of overexpression and reconstitution methods. One approach in particular has recently shown some promise for polytopic integral membrane proteins, and is currently being used in the large scale isolation of MDR proteins for biophysical studies.

Dr. Scheinberg evaluates immunologic approaches to the study and therapy of human leukemia and lymphoma. The overall goals of the Hematopoietic Cancer Immunochemistry Laboratory are to identify and understand the functions of specific cell surface molecules on normal and neoplastic hematopoietic cells and, if possible, to use these molecules as targets for immunotherapy. This includes identification of cell surface targets, development of new immunotherapeutic agents and phase 1 study of these new agents in patients at Memorial Hospital with an emphasis on the use of monoclonal antibodies (mAb) as pharmacologic agents for therapy of leukemia and lymphoma. MAb may be used pharmacologically as carriers of potent toxins or isotopes specifically to tumor cells, as direct mediators of immune cell killing via complement or as regulators of growth via cell surface receptors. Three of our projects focus on applying these approaches to the therapy of human leukemia and lymphomas and one project seeks to identify novel new targets for immunotherapeutics. Currently being studied are: (1) M195, an mAb to CD33, which is restricted to early myeloid progenitors and acute myeloid leukemia (AML) cells; this mAb is active in the treatment of AML; (2) JD118, a cytotoxic mAb, reactive with a B-cell activation antigen and OKB7 mAb reactive with B cell lymphomas and leukemias; (3) MAb JD12, reactive with HLA-A, which blocks T-cell proliferation; (4) the role of glycosphingolipids in B cell differentiation and neoplasia.

Dr. Scotto's laboratory is interested in the role that transcriptional regulation plays in the development and maintenance of the multidrug resistance (MDR) phenotype. In multidrug resistance, which is observed both clinically and in tissue culture, cells that are challenged with vinca alkaloids, actinomycin D or anthracycline antineoplastic agents develop resistance not only to the selective agent but also to a broad spectrum of functionally and structurally unrelated compounds. This resistance is primarily mediated by the overexpression of a plasma membrane protein, P-glycoprotein, which acts as a drug efflux pump. The regulation of the P-glycoprotein genes in human, hamster, mouse and yeast is being investigated with respect to 1) the DNA (cis) elements and protein (trans) factors involved in the altered transcription of this gene in drug-resistant cells; 2) the modulation of P-glycoprotein gene expression during differentiation of secretory cells; 3) the contribution of post-transcriptional and post-translational modifications to the MDR phenotype.

Dr. Sirotnak's research focuses on (1) molecular targets and other cellular biochemical determinants important to selective antitumor action of various categories of cytotoxic antimetabolites; (2) cytoplasmic membrane transport of pharmacologic

agents; (3) molecular mechanisms of acquired resistance of tumor cells to antineoplastic agents; and (4) the regulation of folate and nucleoside transporter gene expression.

Folates play a crucial role in the biosynthesis of macromolecules. Access of tumor cells to exogenous plasma folate is made possible by the existence in the cytoplasmic membrane of a specific high-affinity transport system. Using c-DNA probes, the genetic regulation and molecular biology of this system are now being examined in models which constitutively over-produce or under-produce the transport protein and during induction of tumor cells to terminal maturation.

Folate and nucleoside analogs effectively accumulate in tumor cells via plasma membrane systems normally transporting natural folates and nucleosides. To understand the selective antitumor action of folate and nucleoside analogs, studies are being conducted of the properties and multiplicity of their cellular membrane transport, their interaction with enzymic and macromolecular targets, their intracellular metabolic disposition and their pharmacokinetic behavior. Mechanisms of acquired resistance in tumor cells to these antimetabolites and other cytoxic agents at the level of their cellular membrane transport metabolic disposition and enzymic targets are also studied.

Dr. Szeto's research focuses on 1) maternal-fetal pharmacology of various drugs of abuse; 2) development of opiate compounds for analgesic use during pregnancy that would have minimal adverse effects on the fetus and newborn; and 3) identification of selective opiate agonists and antagonists that may be beneficial in the treatment of infant apnea. Currently being investigated are the pharmacokinetics and pharmacodynamic actions of several opiates, nicotine and marijuana on neurobehavioral, cardiorespiratory and metabolic function in the developing fetus. These studies utilize invasive surgical techniques which permit direct assessment of fetal drug exposure as well as continuous monitoring of various fetal and placental parameters in unanesthesized sheep at different stages of gestation. The sites and mechanisms of action of these compounds can be ascertained using selective routes of drug administration to the fetus, and specific receptor agonists and antagonists. The laboratory's efforts in the development of obstetrical analgesic agents are based on the design of hydrophilic opiate compounds that would have restricted access to the fetus, as well as identifying opiate receptor subtypes that may have analgesic potential without significant actions on placental perfusion or fetal cardiorespiratory function. A large part of the current research effort is spent on studying the ontogenetic development of respiratory control and the role of endogenous opiate peptides in modulating respiratory function in early development. These studies are being carried out in the fetal and neonatal lamb, baboon and human infant. A specific objective of this investigation is to determine the effectiveness of selective opiate agonists and antagonists in enhancing the continuity and stability of the immature breathing pattern which may be beneficial in the treatment of infant apnea and the sudden infant death syndrome.

Dr. Watanabe has a broad interest in various facets of organic chemistry and biochemistry, especially in the development of new chemical reactions and their application to the design of novel molecules that exhibit anticancer and/or antiviral activity, or are useful in elucidating enzyme reaction mechanisms. Many analogues of nucleic acid components and folic acid have been designed and synthesized using new chemistry developed in *Dr. Watanabe*'s laboratory. Some of these compounds showed potent anticancer or antiviral activity and underwent clinical studies. More recently, novel intercalating agents that bear covalent bond-forming capability have been syn-

thesized, some of which showed potent anticancer activity and were found to be potent inhibitors of DNA topoisomerases.

Recently, a simple DNA synthesizer was constructed in *Dr. Watanabe*'s laboratory, and several oligomers derived from synthetic nucleosides have been prepared. The physiochemical and biochemical properties found have been unexpected and intriguing. Using all this information, *Dr. Watanabe* plans to design experiments to explain the complex biological processes and to develop more selective anticancer drugs.

Recent Publications

Bertino, J. R. (with Srimatkandada, S., Schweitzer, B., Moroson, B. A., and Dube, S.), Amplification of a polymorphic dihydrofolate reductase gene expressing an enzyme with decreased binding to methotrexate in a human colon carcinoma cell line, HCT-8R4, resistant to this drug. *J. Biol. Chem.* 264:3524–3528, 1989.

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Gross, S. S. (with Stuehr, D. J., Aisaka, K., Jaffe, E. A., Levi, R., and Griffith, O. W.), Macrophage and endothelial cell nitric oxide synthesis: Cell-type selective inhibition by N^G-aminoarginine, N^G-nitroarginine and N^G-methylarginine. *Biochem. Biophys. Res. Comm.* 170:96–103, 1990.

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Physiology and Biophysics

Faculty

Olaf S. Andersen
Rodney E. Bigler
Walter W. Y. Chan*
Daniel S. Duch
Daniel Gardner
Marvin C. Gershengorn
Bernice Grafstein
Roger L. Greif (Emeritus)
Jason A. Koutcher
Chin OK Lee
Roberto Levi*
Clifton C. Ling
Martin Lipkin
Thomas Maack
Peter R. MacLeish
Lawrence G. Palmer
Thomas G. Pickering
Barbara Rayson
Henry J. Sackin
Jean E. Sealey
John L. Stephenson
Ellen Townes-Anderson
Alan M. Weinstein
Erich E. Windhager

*Members of the Program in Pharmacology. For representative bibliography, see Pharmacology.

Research Activities

The Faculty of the Graduate Program in Physiology and Biophysics offers graduate research training in a wide variety of areas related to understanding function at the molecular, cellular, organ and systems level. The research interests of the faculty are concentrated among the following areas: the structure, function, and regulation of ion channels and other integral membrane transport proteins; intracellular electrolyte homeostasis and renal function, mechanisms of hormone action, receptor turnover, and gene regulation; cardiovascular physiology, nervous and visual system function, development, and regeneration; integrated models of epithelial and renal function; medical physics and radiation biology.

Dr. Andersen is interested in the molecular mechanisms that govern membrane protein structure and function. This general problem is addressed in experiments on membrane-sparring channels. At present, the following issues are under active investigation: how do the primary amino acid sequences encode the conformation of membrane-spanning channels; how do individual amino acid residue substitutions modulate; why do individual channels function in several distinct modes; and what are the mechanisms by which the host bilayer can modulate channel function? The primary techniques used in the lab include: single-channel and other electrophysiological measurements, kinetic analysis, and simulations.

Dr. Duch's laboratory investigates the molecular interactions which define and control the functions of ion channels. This work reconstitutes purified and unpurified sodium channels from the electric organ of the electric eel and the human brain into planar lipid bilayers in order to probe the molecular interactions between the protein and non-protein (carbohydrate and lipid) domains of these channels. These interactions may play important roles in regulating channel function. In a related project, the

mechanisms by which anesthetics modify ion channel function are being examined on a single channel level. These experiments, also conducted with sodium channels in planar lipid bilayers, are designed to probe the intermolecular interactions which define the anesthetic response.

Dr. Palmer's research focuses on the mechanism of transepithelial Na^+ reabsorption by tight epithelia, and the control of this process by hormones and other factors. The nature of the transport system facilitating sodium movement across the apical membrane of epithelial cells is being elucidated using the toad urinary bladder and the mammalian cortical collecting tubule as a model epithelia. Techniques used in Dr. Palmer's laboratory include: patch-clamping, current-voltage analysis, and flux ratio analysis.

Dr. Rayson's research activities center on the investigation of the regulation of synthesis of the Na^+/K^+-ATPase enzyme (the Na^+ pump), a pivotal enzyme in the regulation of intracellular electrolyte levels. In addition, the regulation of the synthesis of renin, a principal determinant of blood pressure and total body fluid and electrolyte balance, is under investigation. Both projects involve analysis of a range of steps within the protein synthetic pathway, employing molecular biological technology.

Dr. Maack's studies are directed to the elucidation of the physiology of cardiovascular hormones and their receptors, as well as the organ and cellular processing of peptide hormones and their receptors. In the past few years, the laboratory has been dedicated to the study of a novel polypeptide hormone, atrial natriuretic factor (ANF). Studies in laboratory elucidated the structure of ANF as well as the main functional actions of the hormone on the kidney and cardiovascular system. More recently, the laboratory discovered that a main class of ANF receptors in kidney and vasculature is involved in the removal of ANF from the circulation and plasma homeostasis of the hormone. Studies are presently under way on the cellular physiology of ANF binding, internalization, lysosomal hydrolysis and on the recycling of ANF receptors in cultured cells. The techniques used in *Dr. Maack*'s laboratory include studies in intact anesthetized and conscious rats, isolated perfused rat kidney, cell culture, receptor-hormone interactions, and general biochemical and physiological techniques.

Dr. Sackin's research interests have focused on the electrophysiology of renal epithelia. Recent work has utilized the patch clamp technique to study single channel and whole cell currents in the proximal tubule and collecting duct of the kidney, with particular emphasis on the role of stretch-activated ion channels. These mechanosensitive channels alter their electrical gating properties as a function of membrane tension. They can act as microtransducers that convert pressure and osmotic information into electrical currents. This may be important for both volume regulation and electrolyte homeostasis, not only in renal epithelia but in other tissues as well.

Dr. Sealey and her colleagues are addressing the question of the coordination of the roles of renin gene expression in the kidney and reproductive organs. They investigate the mechanism whereby tissues that abundantly express the renin gene avoid interference with the circulating renin system in which very low levels of plasma renin are vital for maintenance of blood pressure. *Dr. Sealey* has evidence that the functions of tissue and circulating systems are separated by the actions of two different renins. Active renin continuously forms angiotensin in the circulation. Prorenin, previously thought to function primarily as biosynthetic precursor of renin, has been shown to have its own renin-like activity. Current research focuses on the idea that prorenin catalyzes tissue angiotension formation when it binds to a receptor. This allows separation of the different effects of circulating and tissue renin systems. This

work may lead to the development of specific pharmacologic agents enabling selective blockade of renin system at different target sites.

Dr. Windhager's studies are aimed at elucidating the mechanisms of ion and water movement by renal epithelial cells. The techniques used in Dr. Windhager's laboratory include: isolated perfused renal tubule segments, intracellular measurement of ions by ion selective electrodes, electrophysiological techniques, isolated membrane techniques, and expression of membrane proteins in *Xenopus laevis* oocytes. Current work centers on the role of cytosolic calcium ions as regulators of ion and water transport in proximal tubules and collecting ducts of the kidney.

Dr. Gershengorn's laboratory focuses on the delineation of the mechanism of signal transduction used by thyrotropin-releasing hormone (TRH), which causes simulation of secretion of thyroid-stimulating hormone and prolactin from the anterior pituitary gland, and acts as a neurotransmitter/neuromodulator in the central nervous system. The laboratory has recently isolated a novel cDNA for the mouse pituitary TRH receptor, and identified the receptor as being a novel member of the family of G protein-coupled receptors. Current activities center around two problems: first to define the domains and the specific amino acid residues involved in binding TRH and in coupling to the G protein using receptor mutants and chimeras and molecular modelling; second, to delineate the post-transcriptional mechanism of regulation of the level of TRH receptor mRNA which in turn modulates receptor synthesis.

Dr. Lee investigates the mechanisms by which intracellular Ca^{++}, Na^{+} and H^{+} are regulated and the ion bases underlying changes of contractile force in cardiac muscle cells. He recently demonstrated that the level of intracellular sodium has a profound influence on the contractile force of cardiac muscle via sarcolemmal sodium-calcium exchange. Techniques used in *Dr. Lee*'s laboratory include: single ventricular myocytes and isolated cardiac purkinje fibers, and measurement of intracellular ion activities with ion-selective microelectrodes and intracellular ion activities with ion-selective microelectrodes and fluorescent ion indicators.

Dr. Pickering's main area of research is concerned with development of improved methods for the noninvasive measurement of blood pressure. First, he is using ambulatory monitoring techniques to learn more about the causes of blood pressure variability in normal and hypertensive subjects. This work has shown that most of the observed circadian rhythm of blood pressure can be accounted for by changes of activity. Second, he is analyzing the causes and origins of Korotkoff sounds with a view to the development of a new technique for blood pressure measurement.

Dr. Gardner's laboratory studies how neurons use chemical synaptic transmission to communicate with one another, and how networks of neurons process information. Recent discoveries identify postsynaptic neurons as specifiers of synaptic efficacy, and show that synaptic strengths of invertebrate neurons resemble those in theoretical models. Techniques used by *Dr. Gardner* include electrophysiological voltage- and patch-clamping, computer data acquisition and analysis, and comparison of network behavior of biological and computer-simulated neural networks.

Dr. Grafstein investigates nerve regeneration and transport of material in nerve axons. She is currently studying regeneration of goldfish optic nerve. Some of the conclusions reached in recent work are: phosphorylation of axonally transported proteins is an important function in regeneration; block of physiological activity impairs regeneration by interfering with axonal transport of glycosylated constituents. *Dr. Grafstein*'s laboratory uses the following techniques, among others: isotope tracer studies, electronmicroscopy, high-resolution autoradiography, and 2-dimensional gel electrophoresis.

Dr. MacLeish's research program focuses primarily on the functional organization of the vertebrate retina. Dissociated neurons from adult amphibian and prime retinae are employed to study the electrical properties of identified cells and the physiological properties of synapses formed among the retinal neurons *in vitro*. Voltage-sensitive dyes along with conventional intracellular recording techniques are used to measure electrical activity. A separate area of study is the trans-differentiation of retinal pigment epithelium into neural retina, a process that occurs in adult newts and salamanders. Antibody markers are being generated to describe the regeneration process in more molecular terms and a culture system is being refined to determine the role of soluble factors in regeneration.

Dr. Ellen Townes-Anderson studies adult neurons of the vertebrate retina. Questions concerning synaptic mechanisms and regeneration of adult photoreceptors and secondary neurons are being addressed by examining isolated cells *in vitro*. For instance, the issue of synaptic specifity is being tested using retrogradely labeled neurons and time lapse video microscopy to follow the formation of synapses between identified nerve cells types. Other projects involve the use of confocal and electron microscopy.

Dr. Stephenson is interested in theoretical aspects of transport in biological systems. Much of his recent research centers on transport of water and electrolytes in epithelia and in the kidney. One group of current studies focuses on the relation of medullary concentration gradients and the osmolality of final urine in the mammalian kidney to tubular and vascular permeabilities, flows, and architecture. A second project is to develop a mathematical model of electrolyte transport in the whole kidney, which includes electrolytes (Na^+, K^+, Cl^-, HCO_3^-, H_2PO_4, H^+), glucose urea, protein osmotic forces, hydrostatic pressure, and electrical potential. Approaches to these problems include both computer simulation and the development and theoretical analysis of mathematical models.

Dr. Weinstein is interested in the theory of solute and water transport across epithelia and developing mathematical models that permit the computer simulation of normal and pathological conditions. The primary focus of this work is the study of the proximal tubule sodium reabsorption: the transepithelial pathways and driving forces of sodium transport and the mechanisms by which physical factors modulate this reabsorption. Proximal tubule bicarbonate reabsorption is also examined in simulations of the acid-base disturbances. A second focus of this research has been the dynamics of cell volume homeostasis, with scrutiny of proposed mechanisms for the coordination of solute transport at luminal and basolateral epithelial cell membranes.

Dr. Koutcher's research focuses on *in vivo* applications of nuclear magnetic resonance (NMR) to the study of hematologic and neoplastic diseases. These studies are performed in both animal systems (usually, mice, but also rats) and patients, and will be expanded shortly to tumor cells in culture. The focus of much of the work is to determine whether tumor metabolism, as monitored by *in vivo* NMR spectroscopy, can be used to determine tumor sensitivity to anti-neoplastic therapy, or as an early marker of tumor response. Additional research involves the investigation of agents that sensitize tumors to radiation and chemotherapy such as the radiation sensitizing agent Fluosol-DA. The goal of this work is to determine which tumors are most likely to be sensitized by these drugs. More recently, we have applied ^1H volume localized spectroscopy to study bone marrow in patients with hematologic diseases. These studies are being expanded to animal and cell models.

Dr. Ling is interested in the biological effects of radiation pertaining to radiation carcinogenesis and to the application of radiation for cancer radiotherapy. At present four areas of research are conducted in his laboratory: (1) physical dosimetry as it pertains to clinical radiation oncology, particularly brachytherapy; (2) radiobiology of low energy and short-lived isotopes; (3) radiation-induced oncogenic events in carcinogenesis; and (4) the influence of oncogene expression on cellular radiosensitivity.

Recent Publications

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Windhager, E. E. (with Lin, J. T., Xu, Z. J., Lovelace, C., and Heinz, E.), Effect of Ca on Na-D-glucose cotransport across isolated renal brush-border membranes. *Am. J. Physiol.* 257(*Renal Fluid Electrolyte Physiol.* 26):F126–F136, 1989.

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Requirements and Course Offerings

Admission

Applications

For admission to the Graduate School of Medical Sciences an applicant must (1) have a baccalaureate degree or the equivalent from a college or university of recognized standing, (2) have adequate preparation in the chosen field of study, and (3) show promise of ability to pursue advanced study and research, as judged by his or her previous record.

As a rule, students are admitted to one of the seven programs of the Graduate School of Medical Sciences which are: *Biochemistry, Cell Biology and Genetics, Immunology, Molecular Biology, Neuroscience, Pharmacology,* and *Physiology and Biophysics.* However, the initial affiliation with a program is far from rigid. For example, a student, after developing an awareness of the variety of research projects available for training, may remain in the original program but choose as thesis advisor a faculty member affiliated with another program, or the student may wish to change programs altogether.

Inquiries about graduate study should be addressed to the Associate Dean of the Graduate School of Medical Sciences, 1300 York Avenue, New York, NY 10021.

Candidates may be admitted in September, February, or July, although places in the graduate program for February and July may not be available because of prior commitments to applicants for September admission. Applicants for February or July admission should correspond directly with the respective Program Director regarding the availability of places.

Application material must be completed and returned to the Office of the Graduate School of Medical Sciences together with (1) official transcripts of records from all colleges and universities attended, (2) a statement of purpose of graduate study, and (3) two letters of recommendation from individuals in academic positions who know the applicant professionally. In addition, scores from the Graduate Record Examinations (GRE) are required to aid in the evaluation of an applicant. Application for taking the Aptitude (Verbal, Quantitative, and Analytical) Test and the Advanced Test of the GRE, must be made directly to the Educational Testing Service, Graduate Record Examinations, Box 955, Princeton, NJ 08541.

The proper Institution Code Number to use in your GRE application for the Cornell University Graduate School of Medical Sciences (New York City) is R 2119.

Applications for September or July admission and all credentials, including official transcripts of records from all colleges and universities attended, must be received by the deadline of **February 1.** Because GRE scores are an important part of the application it is of decided advantage to the applicant, to submit these scores by the February 1 deadline.

Applications and credentials for February admission must be received by November 1.

Application fee. A nonrefundable charge of $35 is made for filing an application for admission.

The completed application and all supporting documents are initially screened by the credentials committee of the program to which the student is applying. Applicants who are considered potentially acceptable are usually called for a personal interview. At the time of interview, after discussing his or her interests with the members of the Program, the applicant may tentatively select a major sponsor. If accepted by the Program, an application is forwarded to the Credentials Review Committee and then to the Dean for final decision. A student is formally notified of acceptance for study in the Graduate School of Medical Sciences by a letter from the Dean. An applicant accepted for admission is requested to inform the Graduate School of Medical Sciences of her or his plan to either accept or refuse the offer of admission within one month after the Dean's acceptance letter has been received.

It is the policy of Cornell University to actively support equality of educational and employment opportunity. No person shall be denied admission to any educational program or activity or be denied employment on the basis of any legally prohibited discrimination involving, but not limited to, such factors as race, color, creed, religion, national or ethnic origin, sex, age, or handicap. The University is committed to the maintenance of affirmative action programs which will assure the continuation of such equality of opportunity.

Admission policies are also in conformity with the policy of New York State in regard to the American ideal of equality of opportunity as embodied in the Education Practices Act.

Memorial Sloan-Kettering Cancer Center and Manhattan Skyline, as seen from Cornell Medical College.

Categories

An applicant is accepted by the Graduate School of Medical Sciences (1) as a degree candidate for the M.S. or Ph.D., or (2) as a provisional candidate.

Provisional candidacy provides opportunity for a prospective degree candidate, whose educational preparation is difficult to evaluate, to begin graduate studies. On the basis of the record of accomplishment in the first half of the academic year, the adviser or temporary Special Committee of a provisional candidate may recommend to the Dean that (1) provisional candidacy be changed to degree candidacy, (2) provisional candidacy be continued for the remainder of the academic year, or (3) provisional candidacy be terminated. A maximum of one academic year in the status of provisional candidacy is permitted and credit of a maximum of one residence unit may be allowed on petition, provided there is convincing evidence that performance has been of the same quality as that required of degree candidates.

Special Students

Special students are students who are not degree candidates in the Graduate School of Medical Sciences and who are given permission by the dean to take courses at Graduate School of Medical Sciences. Special students must be degree candidates at other institutions and the courses taken at Cornell must be essential to their degree programs and are not offered by the institutions at which they are matriculated as degree candidates as certified by the institutions. Enrollment as a special student is not intended as preparation for admission to degree programs at Cornell or elsewhere.

Special students are accepted only with the approval of the appropriate Program Chairman. Such students must demonstrate special qualifications in terms of preparation and ability. They must register with the Graduate School of Medical Sciences and must pay all tuition and fees before being permitted to attend lectures or laboratory sessions. Tuition is computed on the basis of the ratio of course hours taken to the total hours of instruction for the academic year (33 weeks of 40 hours). There is a registration fee of $35.

Degree Requirements

Major and Minor Programs

A candidate for the degree of Master of Science is required to register for study in one major and one minor program. Each program decides whether the Special Committee of a candidate for the Ph.D. degree must have two or three programs represented. Accordingly, a candidate for the degree of Doctor of Philosophy is required to register for study in one major and one or two minor programs. At least one of the minors must be outside the area of the major program.

The Special Committee

The general degree requirements of the Graduate School of Medical Sciences are minimal in order to give maximum flexibility in choosing a desirable program of study. The student's program is determined with the aid and direction of a Special Committee, consisting of at least three faculty members chosen by the student from those programs that best fit his or her areas of interest. Satisfactory progress toward a degree is judged by the committee rather than by arbitrary standards imposed by the Graduate School of Medical Sciences. There are no regulations of the Faculty of the Graduate School of Medical Sciences governing the specific content of instruction, courses, or grades to which the Special Committee must subscribe, except those imposed by the programs. The committee is primarily responsible for the candidate's development as an independent scholar and scientist.

No later than four weeks after enrollment, a candidate must file a statement of the major and minor programs elected for study, after which the student must choose faculty members to represent the programs and to serve on a Special Committee. The major sponsor usually advises the student concerning the other selections and chairs the committee. At least one member of the committee must represent a program different from the candidate's major program. Members may agree to serve temporarily during the candidate's first year of residence until the candidate has had the opportunity to become acquainted with areas of research in the programs of his or her choice. On completion of this year of residence, a permanent Special Committee will be formed, the membership of which can be changed with agreement of all members of the old and newly formed committees and the approval of the Dean. The members of the Special Committee decide on the student's program of study and research. They judge whether progress toward a degree is satisfactory and prepare term reports on the candidate for submission to the Dean. The members of the committee serve on all the candidate's examining committees and they approve his or her thesis.

Registration and Course Grades

No student in the Graduate School of Medical Sciences may double-register for an advanced general or professional degree with any other school or college except the Cornell University Medical College.

At the beginning of each term, students are required to register with the Office of the Graduate School of Medical Sciences and to file a registration of courses form indicating all courses they will take. A fee of $10 is charged for late registration.

At the beginning of each course in which the student is enrolling, the student will complete a separate course registration form for the instructor. All courses for which the student registers for credit will be entered in the official record. Grades of graduate students are reported as: Excellent (E), Satisfactory (S), Unsatisfactory (U), Incomplete (I), Absent (Abs.), or Unofficially Withdrawn (W). A grade of Incomplete or Absent cannot be changed later than one term following the one in which the course was taken.

Registration for the summer is required of graduate students who will be engaged in research.

Residence

The Faculty of the Graduate School of Medical Sciences regards study in residence as essential. Each candidate for an advanced general degree is expected to complete the residence requirements with reasonable continuity. A student must register each term from the time of his or her first registration in the Graduate School of Medical Sciences until the student either withdraws or completes a degree (unless a leave of absence has been granted). Full-time study for one-half academic year with satisfactory accomplishment constitutes one residence unit. Two units of residence are the minimal requirement for the master's degree and six units are the minimum for the doctoral degree. However, the time necessary to obtain the degree generally exceeds the minimal requirements. A candidate for the Ph.D. degree must spend two of the last four units of required residence in successive terms on the New York City or the Ithaca campus of Cornell University. No more than seven years may intervene between the time of first registration and the completion of all requirements for the doctoral degree. A student must complete all requirements for the master's degree in four years.

Part-time graduate study, if it is necessitated by off-campus employment noncontributory to the major program of study, is not encouraged. Requests for part-time study must be reviewed by the Executive Committee. If permission is granted for part-time study, the student must be in residence at least half-time.

Transfer of Residence Credit

No residence credit will be granted for study outside the Graduate School of Medical Sciences to fulfill the requirements of the M.S. degree. No commitment can be made about granting residence credit toward the Ph.D. requirements for previous study in another graduate school until after the candidate has entered into residence at the Graduate School of Medical Sciences. At that time, the student's Special Committee may recommend acceptance of study outside the Graduate School of Medical Sciences to the Executive Committee, which will determine the number of residence units to be awarded. No credit can be transferred for study undertaken as an undergraduate or as a special student even in courses designed for graduate students.

A student who has satisfactorily completed two or more academic years of study toward the M. D. degree at the Cornell University Medical College, or another accredited medical school in the United States with a curriculum equivalent to that of the Cornell University Medical College, may transfer a maximum of two units of residence credit after passing an evaluation examination administered by a committee appointed by the Executive Committee of the Graduate School of Medical Sciences.

Summer Research

Registration is required for the summer research term whether or not this effort will be credited toward residence unit accumulation. Students registered for summer research pay prorated tuition only if they are obtaining residence credit. However, no degree candidate is eligible for more than two residence units in any period of twelve consecutive months.

Study *In Absentia*

A candidate for the degree of Doctor of Philosophy may petition for permission to earn residence units for study away from Cornell University while regularly registered in the Graduate School of Medical Sciences. A candidate to whom this privilege has been granted, must register as a Candidate *in absentia* and may work temporarily under the immediate supervision of an individual designated by his or her Special Committee although the candi-

date's program will continue to be directed by the Committee. For study *in absentia,* not more than two residence units may be earned toward fulfillment of the minimal residence requirements for the Ph.D. degree.

Leave of Absence

A candidate who finds it necessary to interrupt the continuity of his or her residence must petition the Dean for an official leave of absence. This written petition must specify the term of absence, state the reason for the requested leave of absence, and be approved by the student's Special Committee.

Candidacy for Degree Only

A graduate student who has fulfilled all degree requirements, with the possible exception of the thesis defense and final thesis submission, who leaves campus and is no longer a full-time student, must request Candidate for Degree Only status, which is in effect until graduation.

Examinations

Three examinations are required by the Faculty of the Graduate School of Medical Sciences: (1) Final Examination for the M.S. degree, (2) Examination for Admission to Doctoral Candidacy, and (3) Final Examination for the Ph.D. degree. Examinations are administered by an Examining Committee consisting of a chairperson appointed by the Dean, the members of the candidate's Special Committee, and, in the case of the Admission to Doctoral Candidacy Examination, one additional member selected from the Faculty of the Graduate School of Medical Sciences or of other institutions. In addition to these examinations, the candidate's major program may require a qualifying examination as part of its evaluation of the candidate after two units of residence have been completed.

For the M.S. degree: The Final Examination may be oral or both oral and written.

For the Ph.D. degree: The Admission to Doctoral Candidacy Examination is both oral and written and certifies that the student is eligible to present a thesis to the Faculty of the Graduate School of Medical Sciences. The examination should be taken after course work is largely finished but before significant thesis research has begun. Accordingly, the usual examination time will be at the end of the second year of residence. The examination may not be taken until two units of residence credit have been accumulated and a minimum of two units of residence credit is required after passing this examination before the final examination can be scheduled. The final examination for the Ph.D. degree is an oral defense of the candidate's thesis. It must be passed within four years after completion of the required residence units, or within seven years from the date of first registration, whichever is earlier.

Thesis

A principal requirement for both the M.S. and the Ph.D. degrees is the presentation of a thesis constituting an imaginative contribution to knowledge. Ordinarily, the thesis is written on a research topic in the candidate's major field of study, under the direction of the chairperson of his or her Special Committee. The time between the thesis defense and submission of the thesis in its final form is limited to 60 days. The faculty requires that the Ph.D. thesis be published in abstract and be recorded on microfilm.

Tuition and Fees

Tuition

Tuition for a student regularly matriculated in the Graduate School of Medical Sciences is $14,100 for the academic year 1991–92 and is payable in two equal parts, the first of which is due at initial registration. Tuition includes fees for matriculation, the student health plan, graduation, and miscellaneous thesis expenses.

Students in the Ph.D.-M.D. program (see p. 66) will be charged Medical College tuition while they are enrolled in medical school.

A student who is to receive partial residence credit (see p. 61) because of employment should apply for proration of tuition on forms obtainable at the Office of the Dean.

Other Fees

In Absentia A student registered *in absentia* pays a fee of $200 each term.

Leave of Absence Students on leave of absence will be required to pay an active-file fee of $200 for each semester, up to a maximum of six semesters, during which they are not registered with the Graduate School. This fee will not be subject to finance charges but must be paid before the student can receive an advanced degree. Petition for waiver of this fee will be considered for students who

have not completed the required number of residence units.

For students on leave of absence, the student health plan will remain in force for 30 days following the commencement of the leave.

Candidacy for Degree Only A student who registers as a Candidate for Degree Only pays a one-time fee of $35.

Any individual who owes money to the University will not be allowed to register or reregister in the University, receive a transcript of his or her record, have his or her academic credits certified, be granted a leave of absence, have a degree conferred and will not be eligible for health services and subsidized housing.

The amount, time, and manner of payment of tuition, fees, or other charges may be changed at any time without notice.

Refunds

Part of the *personally* paid tuition will be refunded if the student obtains official certification of leave of absence or withdrawal from the Graduate School of Medical Sciences during the semester. Students who terminate their registration during a regular term in this manner will be charged tuition from the registration day to the effective date of the certificate as follows: first week, 10 percent; second week, 20 percent; third week, 30 percent; fourth week, 40 percent; fifth week, 60 percent; sixth week, 80 percent; seventh week, 100 percent. No charge will be made if the effective date of leave or withdrawal is within the first six days of the term, including registration day.

Financial Assistance

Students who wish to apply for a Stafford Student Loan or other Federal assistance are required to submit a Graduate and Professional School Financial Aid Service (GAPSFAS) form providing an estimate of financial need.

Application forms can be obtained from the Graduate School Office or from the Educational Testing Service. File the form with the Educational Testing Service, Box 2614, Princeton, New Jersey 08541, and request that the information be sent to Cornell-Code 2267.

Financial assistance is available to qualified applicants. Individual fields may offer predoctoral research fellowships, research assistantships, or teaching assistantships. These positions may provide a stipend in addition to tuition. Information about these positions may be obtained directly from the Program Director at the time of application.

Nationwide competitive predoctoral fellowships are available from the National Science Foundation, the National Research Council, and the Howard Hughes Medical Institute. Information about these fellowships should be requested directly from the appropriate agency.

New York State residents are eligible for several predoctoral fellowships and the Tuition Assistance Program. Application forms may be obtained from the New York Higher Education Services Corporation, Student Financial Aid Section, Tower Building, Empire State Plaza, Albany, NY 12255.

Several other loan programs are available to graduate students. Under these programs, repayment of the principal amount of the loan together with the interest on the loan may be deferred until after graduation. Complete information regarding loan programs may be obtained from the Graduate School Office.

Opportunity for part-time employment is often available in departmental research projects or other activities. Applications should be made directly to individual departments.

Scholarships and Fellowships

Full fellowships are available for graduate students. Recipients of this award become Ph.D. Fellows and will receive a full tuition scholarship and a stipend covering living expenses.

Tuition scholarships are available for students who are not covered by a fellowship. This scholarship fund is administered by the Office of the Dean of the Graduate School of Medical Sciences.

In addition, the following named funds provide support for selected students:

The Vincent Astor Scholarship Fund. Funds for tuition assistance are also derived from the income from a generous gift by the Vincent Astor Foundation to the Graduate School of Medical Sciences and to the Medical College. Allocation of these funds for graduate student tuition assistance is made at the discretion of the Dean of the Graduate School of Medical Sciences.

The Departmental Associates Fellowship was established by the generous contributions of The New York Hospital-Cornell Medi-

cal Center Departmental Associates for the support of a Ph.D. candidate in the Graduate School of Medical Sciences.

Herbert and Lee Friedman Fellowship provides support for an M.D.-Ph.D. student and is funded through income derived from an endowment established by Mr. Herbert Friedman to the Sloan-Kettering Institute.

Lee Friedman Memorial Fellowship. Funds for the support of an M.D.-Ph.D. student are provided by income generated from an endowment to the Sloan-Kettering Institute in memory of Lee Friedman, the wife of Herbert Friedman.

The Harry E. Gould, Sr., Medical and Graduate Student Scholarship. This fund was established by Mr. Gould's son, Harry E. Gould, Jr., in memory of his father, a prominent business and civic leader in the City of New York, who had a long-standing interest in medicine. The income from this endowment provides financial assistance for students of the Medical College and Graduate School of Medical Sciences.

The Mildred and Emil Holland Scholarship. Income from a gift by the Emil and Mildred Holland Philanthropic Fund of the Jewish Communal Fund is used to provide tuition support for an M.D.-Ph.D. student.

The Frank L. Horsfall, Jr. Fellowships are derived from income generated by the Frank L. Horsfall, Jr. Fund and are awarded each year to two outstanding students sponsored by faculty members of the Sloan-Kettering Institute.

Robert W. Johnson, Jr. Charitable Trust. The income on a permanent endowment to the Sloan-Kettering Institute provides a fellowship for an M.D.-Ph.D. student.

The W. A. Keck Foundation Medical Scientist Fellowship. This award is derived from a generous endowment awarded to Cornell University Medical College and provides support for an M.D.-Ph.D. student.

The Frances L. Loeb Medical Scientist Fellowships. These fellowships have been endowed by a gift from Frances L. Loeb and provide support for two M.D.-Ph.D. students at the Cornell University Medical College.

The Shirley L. Marshak Fellowship is funded by income derived from the Shirley L. Marshak Trust for Charities. The Fellowship has been designated for award to a student of the Graduate School of Medical Sciences who is engaged in biomedical research.

The Andrew W. Mellon Foundation Fellowships. A grant by the Andrew W. Mellon Foundation provides fellowship support for M.D.-Ph.D. students selected for the Tri-Institutional Medical Scientist Training Program which is administered jointly by Cornell University Medical College, the Cornell University Graduate School of Medical Sciences, and The Rockefeller University.

The Frank R. and Blanche A. Mowrer Memorial Fund. Financial assistance is available from the income of this fund to one student each year enrolled in the Ph.D.-M.D. or M.D.-Ph.D. program.

The Papanicolaou Medical Scientist Fellowship is funded by income from a bequest from Mary G. Papanicolaou in memory of her husband, Dr. George N. Papanicolaou, and by a gift from an anonymous donor to the Cornell University Medical College. The funds provide support for an M.D.-Ph.D. student.

The Abby Rockefeller Mauzé Medical Scientist Fellowship was established by a gift from the Abby Rockefeller Mauzé Trust. The income provides fellowship support for an M.D.-Ph.D. student.

Louis and Rachel Rudin Foundation. The generous gift to the Sloan-Kettering Institute from the Foundation provides a fellowship for an M.D.-Ph.D. student.

The Surdna Foundation Medical Scientist Fellowship was made possible by a generous grant to the Medical College by the Surdna Foundation. The income from this endowment provides fellowship support for an M.D.-Ph.D. student.

The Iris L. and Leverett S. Woodworth Medical Scientist Fellowship. Funds for the support of an M.D.-Ph.D. student are provided by the income from a generous gift from Dr. Leverett S. Woodworth in his own name and in memory of his wife, Iris L. Woodworth.

Awards and Prizes

The Julian R. Rachele Prize. The income of a fund established by Dr. Julian R. Rachele, former Dean of the Cornell University Graduate School of Medical Sciences, provides for an annual prize to be awarded to a candidate

for the Ph.D. degree for a research paper of which the candidate is the sole or the senior author.

The prize was awarded in 1991 to Anne O'Connell and Bruce Sullenger.

The Vincent duVigneaud Prizes for the presentation of outstanding papers by students of the Cornell University Graduate School of Medical Sciences at the Annual Vincent duVigneaud Memorial Research Symposium.

Recipients of these awards in 1991 were Iris Alroy, John Prescott, Lisa Rubin, Anikó Szabó, and John Zebala.

Student Health Services

The student Health Plan of Cornell University Medical College provides hospitalization and major medical insurance for all registered graduate students. In addition, the Plan provides for ambulatory care at the Student Health Service of The New York Hospital-Cornell Medical Center. Physicians at the Health Service will refer students who require specialized care to clinics of the New York Hospital and to attending physicians when needed.

The cost of medical services provided by the Plan are included in the tuition and fee structure announced by the Graduate School of Medical Sciences each academic year. Students will be issued Plan membership cards and will receive courtesy privileges at The New York Hospital Pharmacy.

Entering students are requested to have a physical examination, chest X-ray and laboratory tests performed by their personal physicians prior to matriculation. The hours of the Student Health Service and a complete statement of Plan benefits will be provided to each graduate student upon arrival.

It is recommended that students purchase insurance coverage for eligible dependents who do not have other insurance available to them. Insured dependents are not eligible for care at the Student Health Service but they will be referred to appropriate members of the Hospital staff for medical treatment.

Students who withdraw from the Graduate School of Medical Sciences will be covered for 30 days from the effective date of withdrawal. Dependent coverage may also be continued for this period, and costs will be prorated from the date of termination. See the Registrar of the Medical College to make such arrangements.

Students on an academic leave of absence from the Graduate School of Medical Sciences will be covered for 30 days after the official commencement date of the leave. Dependent coverage may be continued for this period, and costs will be prorated from the date of termination. Students on medical leave of absence from the Graduate School of Medical Sciences will be fully covered for the duration of the academic year.

Graduating students and their dependents are covered until the last day of the month following the month in which the student was last registered in the Graduate School of Medical Sciences.

Residence Halls

F. W. Olin Hall, a student residence, is at 445 East Sixty-ninth Street directly across from the Medical College entrance on York Avenue. Olin Hall contains a gymnasium, lounges, a kitchen on each student floor, and 200 residence rooms. Each room is a single bedroom-study, but since two rooms share a connecting bath, they are normally used as a suite for two students. The rooms are completely furnished. The student housing fee is $265 per month.

Livingston-Ferrand Apartments, also located on East Sixty-ninth Street, just beyond Olin Hall, have furnished apartments of 1½, 2, 3, and 4 rooms. Kitchen facilities are provided in these apartments. Housing fees begin at $338 per month (utilities not included). These apartments are available to families and upper-class students.

Jacob S. Lasdon House, an apartment residence, is located at 420 East Seventieth Street. This building contains studio, one-bedroom, and two-bedroom apartments, and two squash courts. Apartments are fully furnished, include kitchens, and are centrally air conditioned. Housing fees for students sharing apartments begin at $307 per month including utilities. Fees for families begin at $576 including utilities. These apartments are available to families and upper-class students.

The Rockefeller Scholars Residence at 504 East Sixty-third Street, operated by The Rockefeller University and the Memorial Sloan-Kettering Cancer Center, provides a limited number of studio apartments for married students of the Cornell University Gradu-

ate School of Medical Sciences. The monthly housing fee for these studios, which are fully furnished and contain kitchen facilities, is $530.

Housing in the above facilities is guaranteed for a five-year period from the time of first enrollment.

The fees listed may be changed at any time without previous notice.

Pets are not permitted in student housing.

Special Programs

Application to the Tri-Institutional M.D.-Ph.D. Program

See p. 3 for a description of the program. A successful applicant will demonstrate excellent undergraduate science preparation and a strong commitment to combining an investigative career in the biomedical sciences with clinical medicine. Applicants must satisfy the requirements of each institution. After initial screening, selected candidates will be invited to meet with members of the faculties of the medical and graduate programs.

To complete an application, students must submit the following:

To AMCAS in Washington, D.C.:

1. *AMCAS Application.* A completed AMCAS application form should be sent directly to AMCAS by November 1. The personal data and academic record required are suitable for evaluation by both the medical and graduate schools.

To the Tri-Institutional M.D.-Ph.D. Program, Room F-104, Cornell University Medical College, 1300 York Ave., New York, NY 10021:

2. *M.D.-Ph.D. Application Form.* The Tri-Institutional Program Application Form will be sent when information about the program is requested.
3. *Test Scores.* MCAT scores are required; GRE scores are optional.
4. *Personal statement.* Candidates should submit a personal statement summarizing their research background and scientific interests, as well as reasons for wishing to pursue the combined degree.
5. *Letters of Recommendation.*
   a. Each applicant should arrange to provide either a statement and supporting material from his or her premedical advisory committee, or two letters from undergraduate science faculty members evaluating the candidate's suitability for a career in medicine.
   b. Letters from at least two faculty members evaluating the candidate's research potential should also be submitted.
6. *Application Fee.* A $50 processing fee will be requested when the AMCAS application is received by the Medical College Office of Admissions. This fee can be waived in cases of financial hardship. There is no additional application fee for the M.D.-Ph.D. Program.

Deadline. Applications must be received by **November 30.**

Application to the Ph.D.-M.D. Program

See p. 4 for a description of the program. Students admitted to the program will matriculate as second-year medical students, following successful completion while enrolled in the Graduate School of Medical Sciences (GSMS) of all first-year courses of Cornell University Medical College (CUMC) and of all requirements for the Ph.D. degree.

Application for admission to CUMC can be made either during the academic year preceding the year of anticipated enrollment, or two years prior to enrollment. Students must have passed the Admission to Doctoral Candidacy Examination and at least two major first-year medical school courses by the time application is made. Admission, if granted, will be conditional pending completion of all requirements for the Ph.D. degree and of all remaining first-year medical school courses.

To complete an application, students must submit, **by October 15,** the following documents to the Office of the Dean of the GSMS:

1. A completed application for admission with advanced standing (second year) to CUMC. Application forms are obtainable from the CUMC Admissions Office.
2. An up-to-date transcript from the GSMS showing successful completion of at least two *major* courses of the first-year medical school curriculum (Biochemistry, Gross Anatomy, Cell Biology and Microscopic Anatomy, Physiology and Biophysics, Neuroscience).
3. A plan of study for the remaining years in graduate school, incorporating all courses of the first-year medical school curriculum still to be taken. The plan must show endorsing signatures of the members of the student's Special Committee.

4. Two letters of recommendation, one by the student's major sponsor, and one by another member of the faculty of the GSMS addressing the applicant's suitability for the Ph.D.-M.D. program.
5. Results of the Medical College Admissions Test (MCAT).

The Office of the Dean of the GSMS will review the student's credentials and make a recommendation to the Committee on Admissions of CUMC. After review of the application and personal interviews, this committee will determine the acceptability of the student for the Ph.D.-M.D. program and will inform the student of its decision before June 1.

After completion of the second and third years and the required selectives of the fourth year of the Medical College, students in the program receive credit for their graduate studies to satisfy the elective requirements of the fourth-year Medical School curriculum.

While registered as graduate students, the Ph.D.-M.D. candidate is subject to the tuition schedule of the GSMS. Upon registration at CUMC, the candidate is responsible for the tuition charged by the Medical College (full tuition for the second and third years, and a minimum of 30% of the fourth-year tuition).

Biochemistry

Graduate Program Chairman

Alton Meister, Department of Biochemistry,
Cornell University Medical College,
Room E-106, 1300 York Avenue,
New York, NY 10021, (212) 746-6402.

Graduate Program Director

Daniel Wellner, Department of Biochemistry,
Cornell University Medical College,
Room E-09, 1300 York Avenue,
New York, NY 10021, (212) 746-6409

Graduate instruction is offered leading to the Ph.D. degree. Within the framework of degree requirements and in consultation with the student, the course of study is planned to fit the need of the individual. Although formal course work is required, emphasis is placed on research. Research opportunities exist in various areas of biochemistry including enzymology, structure and function of proteins and nucleic acids, molecular biology, physical biochemistry, and the intermediary metabolism of amino acids, carbohydrates, nucleic acids, and lipids. Entering graduate students usually work for short periods in several of the laboratories of the faculty members of the Program before beginning their thesis research. Students are encouraged to choose challenging fundamental research problems that are on the frontiers of biochemistry.

The laboratories of the faculty members are equipped with virtually all of the instruments and facilities required for modern biochemical research; thus, graduate students are instructed in such methodology as chromatography, countercurrent distribution, radioactive and stable isotope techniques, spectrophotometry, electrophoresis, and analytical ultracentrifugation.

Students who undertake graduate study in biochemistry must have a sufficiently comprehensive background in chemistry to pursue the proposed course of study and must present evidence of knowledge of biology, general experimental physics, mathematics (including differential and integral calculus). Students may remedy deficiencies in these areas during the first year of graduate study. The Graduate Record Examination (the aptitude test and the advanced test in chemistry) is ordinarily required.

Courses

Biochemistry. This course is designed to provide the student with a knowledge of the fundamentals of biochemistry and an appreciation of the molecular basis of biological phenomena. There is an emphasis on the biochemical and molecular events relevant to human health and disease. The course is offered to both graduate and medical students. Topics covered include chemical and physical properties of biomolecules, enzymology, molecular biology, metabolism of carbohydrates, lipids, amino acids, purines, and pyrimidines. Graduate students in the Program in Biochemistry are required to pass this course (or its equivalent). First and second quarters, annually. Dr. Griffith, Dr. Wellner, and staff.

Graduate Biochemistry. This is a research-oriented course which examines in detail the structure of proteins and the experimental methods available for increasing our understanding of these important macromolecules. Topics will include modern methods of protein isolation and structure determination. Also covered will be techniques for studying protein conformation and interaction with ligands such as substrates, coenzymes, and hormones. Graduate students in the Program in Biochemistry are required to pass this course (or its equivalent). Third quarter, annually. Dr. Wellner and staff.

Membrane Biochemistry. This course consists of a series of 15 lectures covering topics on structure-function relationships during membrane biogenesis and cell-cell interactions. Topics include membrane composition, membrane cell biology, physical techniques to study membrane structure, membrane receptors and stimulus-response coupling, membrane pathophysiology, thermodynamics, and the molecular aspects of membrane fluidity. These topics will be taught assuming that students have taken the first year Biochemistry course (or its equivalent). Fourth quarter, 1991–92. Dr. Hajjar.

Biochemistry for M.D.-Ph.D. Students. A course offered jointly by the faculties of the Medical College, Sloan-Kettering Division, and The Rockefeller University. The course is primarily designed for M.D.-Ph.D. students,

but Ph.D. and M.D. students may audit it. The course consists of a series of group seminars/tutorial sessions on protein structure and function, signal transduction, molecular biology and immunochemistry. Primary research papers will be assigned for student/faculty discussion. Participants will meet once a week during the first and second quarters. Offered annually. Dr. Hajjar.

Other Academic Offerings

Introduction to Research. Laboratory rotations in experimental biochemistry dealing with the isolation, synthesis, and analysis of substances of biochemical importance (enzymes, co-enzymes, various metabolites and intermediates), and study of their properties by various chemical and physical techniques. The student obtains this varied research experience by spending approximately two months in the laboratory of each of four faculty members of his or her choice. For incoming graduate students majoring in biochemistry.

Biochemistry Seminars. A seminar series in which students, faculty, and invited scientists from this and other institutions report on progress in their laboratories.

Cell Biology and Genetics

Graduate Program Co-Chairpersons

Donald A. Fischman, Cornell University Medical College, Department of Cell Biology and Anatomy, 1300 York Avenue, New York, NY 10021, (212) 746-6140

Joan Massagué, Sloan-Kettering Institute, 1275 York Avenue, New York, NY 10021, (212) 639-8975

Graduate Program Directors

Paula Traktman, Cornell University Medical College, Dept. of Cell Biology & Anatomy, 1300 York Avenue, New York, NY 10021, (212) 746-6165.

David Bader, Cornell University Medical College, Dept. of Cell Biology & Anatomy, 1300 York Avenue, New York, NY 10021, (212) 746-6149

The Program in Cell Biology and Genetics offers advanced study leading to the Ph.D. degree. The Program is intended to prepare students for a career in basic research and teaching in cell or developmental biology, genetics, molecular biology, or related disciplines.

Course Requirements: In the first two years students are expected to complete a core curriculum of Graduate Biochemistry, Cell Biology, and Molecular Genetics. First-year students also participate in a formal journal club designed to foster skills in literature comprehension and oral presentation. To satisfy the requirements for the Ph.D., the students also select four elective courses chosen to complement their background and develop their interests. At the end of the first year, an oral evaluation of each student is conducted in order to monitor student progress and identify areas of strength and weakness. Students are also urged to participate in a weekly forum in which they and post-doctoral fellows report on their research, and are expected to attend one of the weekly research symposia hosted by the departments of Cell Biology and Anatomy or Cell Biology and Genetics. Although the official transcript contains only pass/fail grades, students are expected to perform at a level corresponding to a B average.

Laboratory Rotations: Students rotate through three laboratories during the first year. Such rotations familiarize students with ongoing research in the Interdivisional Program and provide a mechanism for selection of the thesis sponsor. Written rotation reports also provide practice in the skills of presenting scientific data.

Admission to Doctoral Candidacy: The Program administers this qualifying examination before the end of the second year of residence. The specific format of the examination, which is composed of written and oral sections, is determined by the examining committee. Typically, the written examination covers three or four topics selected by the student and committee, and the oral examination centers around a brief research proposal on a topic chosen by the student and not related to the thesis project.

Courses

Advanced Cell Biology. This course is organized as a combination of biweekly lectures, small group discussions in which students present and discuss key papers in cell biology, and research seminars by experts in

appropriate fields. The course covers topics of current interest in cell biology in the areas of cytoskeleton and cell motility, cell cycle, cytoplasmic organization, cell-cell and cell-extracellular matrix interactions, protein sorting, organelle biogenesis, receptor structure and function and second messenger systems. Offered first and second quarters by Drs. Fischman, Massagué, Pardee, Rodriguez-Boulan, and staff.

Molecular Genetics. Offered jointly with the program in Molecular Biology. See description of course under this program. Offered in 1991–92, Quarters I–IV. Drs. Caudy, Chao, Lustig, Neff, Osley, and Traktman (Quarters I and II); Drs. Ballinger, Dorsett, Jack, Jasin, and Lacy (Quarters III and IV).

Developmental Biology. Principles of descriptive, experimental, and molecular developmental biology are presented, using several animal systems as examples. Early development of the whole organism, and of cells, tissues, and organs are considered. Prerequisites: consent of the faculty. Limited to 15 students. Offered in alternate years; third and fourth quarters in 1992–93. Drs. Bachvarova and Bader.

Practicum in Biological Optics. A workshop in practical aspects of light and electron microscopy. Following a weekly lecture, students conduct specific protocols involved in electron microscopy. Topics covered include: tissue fixation, embedding and thin sectioning; transmission and scanning electron microscopy; shadow-casting of proteins and nucleic acids; immunocytochemistry; fluorescence, phase and interference microscopy; laser-scanning confocal microscopy; image reconstruction; photography. All participants are required to complete an independent project. Prerequisite: Consent of instructors. Course requirements include the completion of an independent project paper. Limited to 10 students. Offered in alternate years; third and fourth quarters in 1992–93. Ms. Cohen-Gould, Dr. Fischman and staff.

Biophysics for Biologists. In this new interdisciplinary course, concepts and methodological approaches in biophysics will be applied to current research problems in cell biology and physiology, emphasizing molecular structure and function. The course will be offered annually with alternating subject material. In 1992, the emphasis will be on protein/nucleic acid structure-function relations and interactions. In 1993, the course will address the structure, dynamics and function of membrane lipids and proteins. Two combined lecture and research paper discussions per week. Fourth quarter, Drs. Andersen, Breslow, Pardee, Roepe, and Scotto.

Genetics. A new course in genetics will be offered which will cover aspects of human genetics in depth. The course will present lectures by the faculty and guest speakers on topics which explore the organization of the human genome, gene mapping and linkage, cytogenetics, genetic factors that contribute to normal human variation, inherited and de novo genetic alterations that lead to disease states, and application of genetic knowledge to clinical medicine. Dr. Chaganti and staff. Offered in alternate years; first and second quarters in 1991–92.

Journal Club Seminar for First-Year Students. This seminar is given jointly with the Program in Molecular Biology. See description under this program. Third and fourth quarters annually. Drs. Caudy and Sheffery.

Graduate Student Seminar. This informal seminar is designed to improve graduate students' skills in public presentation. On a rotating basis, students prepare an oral presentation on their research or on a topic of their choice. The presentation is informally critiqued by the faculty. First through fourth quarters, annually. Dr. Robert Benezra.

Cell Biology and Microscopic Anatomy. Offered by the Staff of the Program in Cell Biology and Genetics in conjunction with the Faculty of the Cornell University Medical College. This course follows a cellular and differentiative approach aimed at understanding the structure-function correlates that characterize the different tissues and organs. Lectures are complemented by small-group discussions and laboratory exercises designed to provide students with the skills to study and analyze cells and tissues. A microscope slide collection, presenting tissues and organs in a variety of physiological and developmental states, as well as correlative electron micrographs, are provided for individual study in the laboratory. Second and third quarters, annually. Drs. Traktman and Chao.

Gross Anatomy. Regional anatomy is studied principally through dissection of the human body. Supplementing this technique are prosections by instructors, tutorial group discussions, and radiographic and endoscopic

demonstrations. Enrollment is limited and students should consult the staff early in order to determine the availability of places. First and second quarters, annually. Drs. Hagamen, Weber, and the staff.

Immunology

Graduate Program Chairman

Kenneth O. Lloyd, Sloan-Kettering Institute, Kettering Laboratory, 1275 York Avenue, New York, NY 10021, (212) 639-2257

Graduate Program Director

Janet S. Lee, Sloan-Kettering Institute, 1275 York Avenue, New York, NY 10021, (212) 639-8252

The program of study is developed for each student individually on the basis of the student's interest and prior experience. Immunology students generally take a core of formal courses offered by the graduate school in immunology, biochemistry, molecular biology, cell biology and genetics in order to complement their previous background and fulfill their own academic objectives. Participation in a graduate student seminar course is expected of all students to provide experience in oral presentation. Admission to Doctoral Candidacy at the end of the second year requires both written and oral examinations of the candidate's general understanding of immunology and related subjects which are relevant to the proposed research. However, the main focus of the graduate program in immunology is on laboratory research. Each student is required to undertake at least two minor research projects with different faculty members prior to developing a major research proposal for the doctoral thesis. This allows for laboratory experience to begin during the first year of the student's program. By the third year the doctoral candidate begins a full-time thesis project which typically takes two to three years. During this time the student will continue to participate in the other educational programs offered by the Institute. These include a wide variety of research seminars which are offered throughout the year with speakers from outside the Institute. In addition, the Immunology Program offers a series of colloquia on current topics in immunology with presentations and discussions led by Immunology faculty members.

Applicants should have a strong undergraduate background in the biological sciences, including biochemistry, molecular genetics, and microbiology and are also expected to have some undergraduate laboratory research experience. The application requires a personal statement describing the student's background and specific interest in the Immunology Program. An official transcript of the student's undergraduate record is also necessary with at least two letters from faculty members who can evaluate the academic potential of the student in a Ph.D. program in Immunology. Applicants must also submit the results of the Graduate Record Exam including the advanced test in Biology or Chemistry.

Courses

Immunology. This course provides a comprehensive overview of basic immunology with a focus on recent developments in many areas. There is an emphasis on current papers and experimental approaches to the study of immunology.

Topics include techniques in immunology, B lymphocytes, immunoglobulins and monoclonal antibodies, T lymphocytes and T-cell clones, immunogenetics of lymphocyte differentiation antigens, cell mediated immunity, T cell antigen receptors, natural cytotoxicity, macrophage and other accessory cells, lymphokines, and the major histocompatibility complex genes. Quarters I and II, annually. Dr. Lee and the Immunology Program Faculty.

Other Academic Offerings

Colloquia in Immunology. Informal sessions are held monthly between students and senior faculty members to acquaint students with the major research programs headed by each of the faculty members of the Immunology Program.

Student Seminar Series. Graduate students have an opportunity to present their work in an informal setting. Quarters I–IV, annually.

Molecular Biology

Graduate Program Chairman

Kenneth I. Berns, Department of Microbiology, Cornell University Medical College, Room B-308, 1300 York Avenue, New York, NY 10021, (212) 746-6505

Graduate Program Director

Elizabeth Lacy, Sloan-Kettering Institute, Rockefeller Research Laboratories, Room 917A, 1275 York Avenue, New York, NY 10021, (212) 639-8661

Admission: A good background in genetics, molecular biology, chemistry, or biochemistry is required of students. Graduate Record Examination scores in both the aptitude test and an advanced test (biology, chemistry, or biochemistry, cell and molecular biology) are also required.

Course Requirements: Students must complete a core sequence of Graduate Biochemistry, Molecular Genetics, Eukaryotic Gene Structure and Function, and Journal Club Seminar during their first year. In addition, students participate in the Graduate Research Seminar throughout their enrollment. To complete the course requirements, eight additional quarter-equivalents of coursework must be taken before graduation chosen from a list of courses approved by the Curriculum Committee. This list currently includes: Nucleic Acids Enzymology, Cell Biology, Developmental Biology, Molecular Virology, Molecular Biology of Growth Control and Neoplastic Transformation, Electron Microscopy, and Immunology.

Laboratory Rotations: Students are required to rotate through three laboratories. Laboratory rotations begin immediately after a series of lectures by the faculty designed to familiarize students with the research underway in their laboratories. Rotation periods are: October–January, February–May, June–August. It is expected that students will have chosen their thesis mentor by the start of their second year in the program.

Admission to Doctoral Candidacy: This examination will be given twice each year, in April and September. It will consist of two parts, a uniform written exam and an oral defense of a written research proposal. The proposal cannot be in the same field as the student's thesis research. It is expected that most students will take this exam during their second year.

Special Committee: A student's Special Committee will be chosen by the student in consultation with his/her mentor when the student selects a laboratory for thesis research. The function of the Special Committee is to evaluate the direction and progress of a student's thesis research and to serve as an informational resource for the student.

Curriculum Committee: This committee, chaired by the Program Director and consisting of 8–10 members of the faculty, oversees all educational aspects of the program. The committee is responsible for assembling the curriculum, setting course requirements, adjudicating student applications for exemption from course requirements, and composing and administrating of the Admission-to-Candidacy Examination.

Courses

Eukaryotic Gene Structure and Function. A semester-long course presenting the fundamentals of eukaryote gene structure, expression and regulation. Topics discussed include: DNA sequence organization, chromatin structure, viral and cellular RNA transcription, translation and its regulation, control of gene expression in model systems and molecular aspects of carcinogenesis. Third and fourth quarters, annually. Dr. Freedman and staff.

Nucleic Acids Enzymology. A formal course presenting the enzymological mechanisms and control of prokaryotic and eukaryotic transcription and DNA replication. Enzymes which alter DNA structure and shape are reviewed and topics in DNA repair and recombination are also covered. Graduate Biochemistry is a prerequisite. First and second quarters annually. Drs. Marians, Hurwitz, Rabkin, Holloman, and O'Donnell.

Molecular Virology. A formal course in which major emphasis is placed on the basic mechanisms in the biology of all animal viruses, including RNA and DNA tumor viruses. The topics considered include virus structure and composition, assay of viruses and viral-specific products, transcription and replication of viral nucleic acids, translation of virus-specific proteins, assembly of viral particles, structural and functional alterations in viral-infected cells including transformation, pathogenesis of viral diseases, and viral genetics. Alternate years. Offered third and fourth quarters, 1992–93. Drs. Hayward, Besmer, Traktman, Lusky, and staff.

Molecular Genetics. This course, which is offered jointly with the Program in Molecular Biology, focuses on key topics of molecular genetics in bacteria and bacterial viruses, yeast, nematodes, *Drosophila,* and mouse. The isolation of mutants and their analysis by recombination, complementation and the generation of suppressors are discussed in

depth. The course consists of lectures and interactive small-group discussions of research papers from the current literature. Limited to 36 students. Offered in 1991–92 as two sequential two-quarter courses with the first focusing on prokaryotic and simple eukaryotic systems, and the second covering complex eukaryotic systems and special topics. Drs. Caudy, Chao, Lustig, Neff, Osley and Traktman (quarters I and II); Drs. Ballinger, Dorsett, Jack, Jasin and Lacy (quarters III and IV).

Molecular Biology of Growth Control and Neoplastic Transformation. This course focuses on current efforts to understand the neoplastic cell phenotype from a molecular point of view. The effects of RNA and DNA tumor viruses on host cells are discussed, in particular the transformation and/or differentiation blocks of defined cell lineages by certain agents. The nature and enzymatic specificities of viral gene products responsible for transformation are compared with related products of normal cellular genes. The potential interaction of such products with regulatory systems controlling cell shape, adhesiveness, motility, and mitosis are described, as well as the possible involvement of the same systems in nonviral neoplasias. A section of the course is devoted to the molecular biology and biochemistry of cell surface growth factor- and polypeptide hormone-receptors and mechanisms of signal transmission across biological membranes. At least part of the course consists of student presentations on relevant subjects. Third and fourth quarters, alternate years. Offered in 1991–92. Drs. Hayward, Besmer, and Brown.

Graduate Research Seminar. This course represents an opportunity for all the faculty and students of the program to hear the upper-class students describe their research in formal seminar presentations. Quarters I–IV, annually. Dr. Lacy.

Journal Club Seminar for First-Year Students. This seminar is designed to give first-year students a chance to improve their skills in presenting and analyzing scientific data. Each student presents two papers during the semester. Papers are chosen by the students and approved by the instructors. Speakers generally provide a brief relevant background and then present each figure in the paper, summarizing the experimental method or assay used, the results illustrated, and the conclusions drawn. Participation by all students is encouraged during the presentation. Given jointly with the Program in Cell Biology and Genetics. Annually, third and fourth quarters, Drs. Caudy, O'Donnell, Sheffery, and Shuman.

Neuroscience

Graduate Program Chairman

Fred Plum, Department of Neurology and Neuroscience, Cornell University Medical College, Rm. A-569, 1300 York Avenue, New York, NY 10021, (212) 746-6575

Graduate Program Director

Gavril Pasternak, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, (212) 639-7046.

The Program in Neuroscience provides training in the study of the nervous system. It includes the disciplines of neuroanatomy, neuroembryology, neurophysiology, neuropharmacology, neurochemistry, neuroendocrinology, molecular biology, and neuropsychology and perception. The program emphasizes a multidisciplinary approach to the study of the nervous system, based on the belief that future advances in our understanding of the nervous system will be derived from the thinking and research techniques employed by more than one discipline. Toward this end, the program of entering students is planned in consultation with several staff members, and the students are expected to spend some period of time working closely with members of the faculty whose interests are related to theirs. In addition, there are regularly scheduled seminars during which various aspects of work in process are presented and discussed. By these means, the students are afforded the broadest possible view of the program during their total training experience.

The student majoring in Neuroscience will be required to satisfy the requirements of the courses in neuroscience and biostatistics and courses in physiology, biochemistry, pharmacology, and genetics as determined by consultation with the major and minor advisors. In addition, participation in the seminar program and advanced course offerings is required. Advanced course offerings will change from year to year. While there are no language requirements, it is suggested that the student achieve mastery of a modern foreign language or a computer programming language. The student choosing Neuroscience as a minor is required to participate in the neuroscience course and the seminar program as well as obtain any additional experience that the minor sponsor may suggest.

Applicants to the program are expected to have had adequate undergraduate training in biology, organic chemistry, physics, and mathematics. Graduate Record Examination scores are to be submitted with the application. An interview with the applicant is considered highly desirable.

Courses

Neuroscience. This is the basic undergraduate medical school course and is required of all major and minor candidates in the program. It is a broadly based course and introduces the student to neuroanatomy, neurophysiology, and pertinent neurology. Fourth quarter annually. Drs. Brooks and Grafstein.

Cellular Neuroscience. A required course for all major candidates and a prerequisite for the medical school Neuroscience course. It will cover fundamental concepts about membrane potential, nerve cell structure, and neurochemistry and provide an introduction to the problems of nerve cell degeneration, plasticity, and behavior. Third quarter, 1991–92. Dr. Townes-Anderson and the faculty of the Neuroscience program.

Neuroscience Seminar. Current topics of neurosciences, not included or minimally covered in the Neuroscience course, are examined in detail. Fourth quarter with adequate enrollment. Drs. Brooks and Grafstein.

Neuropharmacology. See Program in Pharmacology.

Proseminar in Synaptic Physiology. The physiology and biophysics of synapses are explored by reading and discussion of seminal papers in the original literature. The first half of the course examines a model synapse, the mammalian neuromuscular junction, by intracellular recording, voltage clamping, noise analysis, and patch-clamping. Topics in the second half include NMDA receptors, plasticity, and neural networks. Fourth quarter, 1991–92. Dr. Gardner.

Chemical Neuroanatomy. This course is designed to orient students to understanding the chemical pathways of the brain. The course will discuss contemporary methods, major transmitter systems and when possible will consider pharmacological and pathological conditions. Neuroscience course, prerequisite. To be offered third quarter, 1991–92. Drs. Milner and Aoki.

Mathematical Structures in Neuroscience. The aim of this course is to provide a didactic introduction to a variety of mathematical structures. The structures are selected both because of their proven usefulness and their intrinsic interest. The emphasis will be on concepts, techniques, and examples. Important theorems will be discussed, but in general, not proven. Rather, they will be illustrated through application, and also through counterexamples of would-be stronger theorems. First quarter, 1992–93, with adequate enrollment. Dr. Victor.

Molecular Basis of Neurological Disease. This course will review current attempts to understand neurological disease from a molecular point of view. Students will develop an understanding of the basic mechanisms of gene expression and will learn how to apply these concepts to the study of neurological disease. Topics will include muscular dystrophy, myasthenia gravis, Alzheimer's disease, Huntington's disease and brain tumor biology. The course will consist of both lectures and informal discussions of recent research papers. First quarter, 1991–92, with adequate enrollment. Dr. Furneaux.

Pharmacology

Graduate Program Co-Chairpersons

Joseph R. Bertino, Sloan-Kettering Institute, Rockefeller Research Laboratories, Room 601, 1275 York Avenue, New York, NY 10021, (212) 639-8230

Lorraine J. Gudas, Department of Pharmacology, Cornell University Medical College, Room E-409, 1300 York Ave., New York, NY 10021, (212) 746-6250

Graduate Program Director

Charles E. Inturrisi, Department of Pharmacology, Cornell University Medical College, Room LC-524, 1300 York Ave., New York, NY 10021, (212) 746-6235

The Program in Pharmacology brings together faculty members from the Department of Pharmacology, Cornell University Medical College and the Program of Molecular Pharmacology and Therapeutics of the Sloan-Kettering Institute for Cancer Research. This interdisciplinary faculty provides the student

with a broad spectrum of research opportunities and advanced courses in pharmacology.

Admission: A strong background in the natural sciences and/or health sciences is required for admission. Graduate Record Examinations in both the aptitude test (verbal, quantitative and analytical) and the advanced test in Biology or Chemistry are also required.

Course Requirements: In the first two years students are expected to complete a core curriculum that may include the following courses: Introduction to Pharmacological Principles, Biochemistry, Graduate Biochemistry, Cell Biology and Microscopic Anatomy, Physiology and Biophysics, Neuroscience, General Pharmacology, Molecular Pharmacology, Neuropharmacology, and Pharmacology Research Seminar.

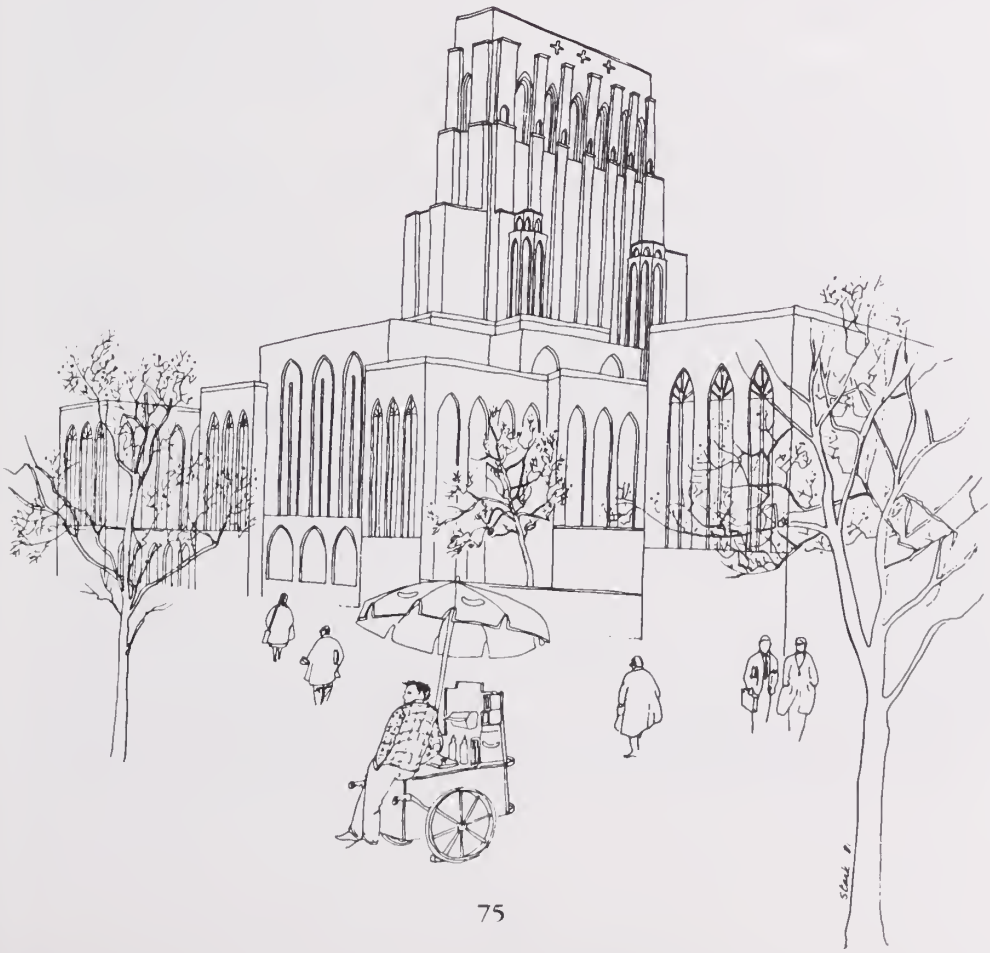
Program Supervision and Laboratory Rotations: The Program Director and the Curriculum Committee will supervise the student's graduate program until the student selects a faculty member to serve as the major sponsor. Three laboratory rotations are required of each student. These rotations provide the opportunity for the student to participate in the diverse research activities that are available within the Program. This experience is designed to assist the student in the selection of major and minor sponsors for the thesis research.

Admission to Doctoral Candidacy: This examination consists of two parts: a uniform written exam and an oral exam which includes discussion of a written research proposal. It is expected that most students will take this exam by the end of May of their second year.

Special Committee: The Special Committee includes a major faculty sponsor and two minor faculty sponsors. The Program Director will assist the student in the selection of the major (thesis) advisor.

Courses

Introduction to Pharmacological Principles. This course is designed to introduce



the student to concepts unique to pharmacology. The introductory course will emphasize general concepts in receptor theory, the dose-response relationship, mechanisms of drug action and resistance, pharmacokinetics, metabolism, tolerance and dependence. All first-year graduate students in pharmacology are required to take this course, which is also open to all students in the graduate school. First quarter, annually. Dr. Pasternak and staff.

General Pharmacology. This basic pharmacology course consists of lectures, demonstrations, and small group conferences. The purpose of these exercises is to teach the principles of pharmacology to second-year medical students and to graduate students. Detailed consideration is given to the parameters of drug action to provide the student with the fundamental concepts essential for evaluation of any drug. Consequently, the scientific basis of pharmacology is emphasized. Prototype drugs, essentially considered systemically, serve to illustrate several mechanisms and parameters of drug action. Therapeutic applications are considered insofar as they illustrate principles of pharmacology or drug hazards. Second and third quarters, annually. Dr. Chan and staff.

Neuropharmacology. This course presents the neuropharmacology of selected drugs and chemical substances that affect the central nervous system. Emphasis is placed on molecular mechanisms of drug actions with regard to the biochemistry and physiology of nervous tissue. This includes mechanisms of neurotransmitter action, and drug actions that modify neurotransmitter actions. Several pharmacologic concepts important to understanding drug action on the nervous system are considered throughout, including selectivity, specificity, dose-response and receptor theory, tolerance, physical dependence and drug abuse. Offered 1991–92, fourth quarter. Drs. Okamoto, Inturrisi and staff.

Molecular Pharmacology. This course examines drug action at the molecular level. Topics include: interaction of drugs with macromolecules; drug resistance; membrane transport; regulation of gene expression; gene transfer; novel mechanisms of drug delivery, antiviral agents, antisense and monoclonal antibody therapy. Offered 1992–93, fourth quarter. Drs. Bertino, Scotto and staff.

Pharmacology Research Seminar. Topics of contemporary pharmacological interest and new concepts and methodological approaches in biological research will be presented by guest speakers, faculty members or students. The presentations are followed by a discussion session which provides an opportunity for students to meet and talk to leading scientists in the field. Details of events will be announced in advance. First through fourth quarters, 1991–92. Dr. Szeto.

Other Academic Offerings

Research in Pharmacology. Research opportunities may be arranged throughout the year for graduate students who are not majoring in pharmacology but who want some investigative experience in the discipline. Special opportunities are offered for work on the nervous and cardiovascular systems and in biochemical and clinical aspects of pharmacology.

Journal Club. This course is designed to improve graduate students' skills in public presentation. On a rotating basis, students prepare an oral presentation on a topic of their choice. The presentation is informally critiqued by the faculty. First through fourth quarters, annually; see the Program Director for further information.

Physiology and Biophysics

Graduate Program Chairman

Erich E. Windhager, Department of Physiology and Biophysics, Cornell University Medical College, Room C-508, 1300 York Avenue, New York, NY 10021, (212) 746-6358

Graduate Program Director

Olaf S. Andersen, Department of Physiology and Biophysics, Cornell University Medical College, Room LC-501, 1300 York Avenue, New York, NY 10021, (212) 746-6350

Opportunities are offered toward the Ph.D. degree in several areas of physiology and biophysics. Ample space is available, and laboratories are well equipped to provide predoctoral training in a medical environment. Interested individuals are urged to contact the Program Chairman before preparing a for-

mal application. Letters of inquiry should include a discussion of the educational background and indicate possible areas of emphasis in graduate study. There has been a tendency to encourage applications from individuals who have a probable interest in more than one of the areas of physiology represented within the program.

Admission: Applicants must have completed courses in biology, inorganic and organic chemistry, physics, and mathematics through the level of differential and integral calculus. Additional course work in these disciplines at the undergraduate level is encouraged. Graduate Record Examination scores in both the aptitude test and an advanced test (biochemistry, biology, cell and molecular biology, chemistry, or physics) or an equivalent test is also required. Applicants from abroad are, in addition, required to take the TOEFL examination. Applicants with otherwise exemplary records who lack certain course requirements will be considered for acceptance provided that they remedy deficiencies while in training.

Course Requirements: The course of study emphasizes the importance of teaching and research in the preparation and development of individuals for careers in physiology. This goal is achieved by a combination of didactic courses, seminars, and closely supervised research leading toward the preparation of a satisfactory thesis.

A special program of study will be developed for each student in consultation with his or her Special Committee.

1. In the first two years students are expected to complete a course curriculum that may include: biochemistry, cell biology, molecular biology and genetics, neuroscience, pharmacology and physiology and biophysics.
2. In addition, students will during the first two years have two or three laboratory rotations of about three months duration. A thesis advisor is chosen by the summer of the first year, and a Special Committee consisting of this major research advisor and two minor advisors is constituted to guide students in their research preparation. Students start their thesis research before completing their formal coursework, but they are not admitted to Ph.D. candidacy before passing the Admission to Doctoral Candidacy Examination towards the end of the second year.

Courses

Physiology and Biophysics. Lectures and conferences on body fluids, bioelectric phenomena, endocrinology, and circulation. Third quarter, annually. Dr. Windhager and staff. Endocrinology is taught as an interdisciplinary course during two weeks (from 9 to 5) of this quarter using hours normally allocated not only to courses in physiology, but also in cell biology, and biochemistry. Course coordinator: Dr. Greif.

Lectures and conferences on respiration, kidney function, acid-base regulation, and gastrointestinal function; and a weekly laboratory on selected aspects of physiology. Fourth quarter, annually. Dr. Windhager and staff.

Topics in Membrane Physiology. This weekly 2-hour conference is designed for Ph.D. and M.D.-Ph.D. students with a major or minor in Physiology and Biophysics. It is at a somewhat advanced level, especially in its quantitative approach to physiology. The aims of the conference are to train students in physiological concepts, to facilitate the understanding of lecture material in the Physiology and Biophysics course, and to establish close student-faculty contact. Third quarter, annually. Dr. Andersen.

Ionic Channels. The course covers mathematical and experimental approaches to the topic of ion movement through single channels. Minimum of 5 students. Prerequisite: 2 years of calculus. Fourth quarter, annually. Dr. Andersen and invited lecturers.

Mathematical Models of Membrane Transport. The general, thermodynamic description of membrane and epithelial transport will be reviewed (with reference to Katchalsky, Curran and Schultz, Sauer, Essig and Caplan). Comparison with kinetic descriptions of membrane transport will be considered (Heinz, Hill). The analysis of composite membrane systems will be examined (Kedem and Katchalsky) as a prelude to the construction of epithelial simulations (Sackin and Boulpaep, Weinstein and Stephenson). Examples of such simulations will be used to examine transport along the kidney tubule under normal and pathological conditions. Third and fourth quarters, annually. Dr. Weinstein.

Selected Topics in Kidney and Electrolyte Physiology and Pathophysiology. Lectures, seminars and demonstrations. Topics

include: 1) GFR, clearance concept, reabsorption and secretion of electrolytes; 2) concentrating mechanism; 3) electrophysiology of the nephron; 4) pathophysiology of potassium; 5) renal hemodynamics; 6) control of body fluid volume and tonicity; 7) control of acid base balance; 8) pathology and pathophysiology of renal failure. Minimum of 8 students. Fourth quarter, annually. Drs. Maack, Windhager and staff.

Physiology of Cardiac Muscle. The course is designed to present cellular mechanisms which are involved in the fundamental processes of excitation and contraction of cardiac muscle. Topics include: 1) action potential; 2) ion transport; 3 contractility (positive and negative inotropic effects); 4) excitation-contraction coupling; 5) arrhythmias; 6) cardiac
failure. One laboratory day is planned for demonstrations of changes in action potential and twitch tension by inotropic agents. Minimum of 5 students. Prerequisites: third-quarter physiology or equivalent. Fourth quarter, annually. Dr. Lee and invited lecturers.

Topics in Gastrointestinal Physiology. Lectures and seminars. Topics include: 1) functional morphology of stomach and intestine; 2) proliferation and differentiation of gastrointestinal cells; 3) motility of esophagus, small intestine and colon; 4) gastric and intestinal secretion; pancreatic secretion; 5) lipid absorption; 6) intestinal absorption of calcium and vitamin D; 7) structure and function of bile acids; 8) gastrointestinal hormones. Minimum: 8 students. Fourth quarter, annually. Dr. Lipkin and invited experts in the field.

Biophysics for Biologists. See description under Cell Biology and Genetics. Fourth quarter, annually. Drs. Andersen, Breslow, Pardee, Roepe, and Scotto.

Proseminar in Synaptic Physiology. See description under Neuroscience. Fourth quarter, annually. Dr. Gardner.

Register

University Administration

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Robert Michels, Provost for Medical Affairs and Dean of the Medical College

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Graduate School of Medical Sciences

Administration

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Bernard L. Horecker, Dean of the Graduate School of Medical Sciences, Associate Dean of the Graduate School

Dieter H. Sussdorf, Associate Dean of the Graduate School of Medical Sciences, Assistant Dean of the Graduate School

Richard A. Rifkind, Director, Sloan-Kettering Division

Standing Committees

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Kenneth I. Berns
Joseph R. Bertino
Donald A. Fischman
Lorraine J. Gudas
Charles E. Inturrisi
Elizabeth Lacy
Kenneth O. Lloyd
Joan Massagué
Alton Meister
Robert Michels
Clarissa Naftzger*
Fred Plum
Richard A. Rifkind
Dieter H. Sussdorf
Erich E. Windhager
Yoram Vodovotz*

Faculty Advisory Committee

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Elizabeth Lacy
Janet S. Lee
Robert Michels*
Gavril N. Pasternak
Richard A. Rifkind*
Julie Rudnicki
Dieter H. Sussdorf*
Paula Traktman
Daniel Wellner

Curriculum Committee

Donald A. Fischman, Chair
David B. Donner
Bo Dupont

Alton Meister
Tong H. Joh
Richard A. Rifkind
Francis M. Sirotnak
Dieter H. Sussdorf
Erich E. Windhager

Graduate Student Executive Council

Yoram Vodovotz, Chair
Zeynep Altun
Avery August
John Corradi
Rita Ghosh
Issam Halaby
Clarissa Naftzger
Hong Peng
S. Craig Rochester
Peter Romanienko
Julie Rudnicki
Valerie Schadlow
John Wittschieben

Graduate Student/Faculty Liaison Committee

Avery August, Chair
Rita Ghosh
Bernard L. Horecker*
Kenneth J. Marians
Joel D. Pardee
Hong Peng
Valerie Schadlow
Dieter H. Sussdorf*

*nonvoting member

Faculty

Albino, Anthony P., Assistant Professor of Immunology. B.A. 1970, Hunter College of the City University of New York; Ph.D. 1974, Cornell University

Alonso, Daniel R., Professor of Pathology. M.D. 1962, University of Cuyo (Argentina)

Andersen, Olaf S., Professor of Physiology and Biophysics. Candidatus Medicinae 1971, University of Copenhagen (Denmark)

Anderson, Mary E., Assistant Professor of Biochemistry. B.A. 1977, Hollins College; Ph.D. 1983, Cornell University Graduate School of Medical Sciences

Aoki, Chiye, Assistant Professor of Neuroscience. B.A. 1978, Barnard College, Columbia University; Ph.D. 1985, The Rockefeller University

Bachvarova, Rosemary F., Professor of Cell Biology and Anatomy. B.A. 1961, Radcliffe College; Ph.D. 1966, Rockefeller University

Bader, David M., Associate Professor of Cell Biology and Anatomy. B.A. 1974, Augustana College; Ph.D. 1978, University of North Dakota

Baker, Harriet D., Associate Research Professor of Neuroscience. B.A. 1963, Wells College; M.S. 1967, University of Illinois; Ph.D. 1976, University of Iowa

Ballinger, Dennis G., Assistant Professor of Molecular Biology. B.A. 1978, University of Colorado; Ph.D. 1984, Massachusetts Institute of Technology

Barany, Francis, Associate Professor of Microbiology. B.A. 1976, University of Illinois at Chicago Circle; Ph.D. 1981, The Rockefeller University

Benezra, Robert, Assistant Professor of Cell Biology and Genetics. B.A. 1975, University of Rochester; M.A. 1982, Ph.D. 1986, Columbia University

Berns, Kenneth I., The R.A. Rees Pritchett Professor of Microbiology. Professor of Microbiology in Pediatrics. A.B. 1960, Ph.D. 1964, M.D. 1966, Johns Hopkins University

Bertino, Joseph R., American Cancer Society Research Professor. Professor of Molecular Pharmacology and Therapeutics. Professor of Medicine. Professor of Pharmacology. B.S. 1950, Cornell University; M.D. 1954, Downstate Medical Center

Besmer, Peter, Professor of Molecular Biology. M.S. 1964; Ph.D. 1969, Eidgenössische Technische Hochschule (Switzerland)

Bianco, Celso, Adjunct Professor of Cell Biology and Anatomy. M.D. 1966, Escola Paulista de Medicina (São Paulo, Brazil)

Biedler, June L., Professor of Cell Biology and Genetics. A.B. 1947, Vassar College; Ph.D. 1959, Cornell University

Bigler, Rodney E., Associate Professor of Physics in Radiology. B.S. 1966, Portland State College; Ph.D. 1971, University of Texas

Black, Ira B., Adjunct Professor of Neurology and Neuroscience (Robert Wood Johnson Medical School). A.B. 1961, Columbia College; M.D. 1965, Harvard University

Blasberg, Ronald G., Professor of Neurology. B.A. 1961, Colgate University; M.D. 1967, Albert Einstein College of Medicine

Blass, John P., The Winifred Masterson Burke Professor of Neurology. Professor of Medicine. A.B. 1958, Harvard University; Ph.D. 1960, University of London (United Kingdom); M.D. 1965, Columbia University

Boskey, Adele L., Professor of Biochemistry. B.A. 1964, Barnard College; Ph.D. 1970, Brown University

Bovbjerg, Dana H., Assistant Professor of Immunology. Assistant Professor of Immunology in Neuroscience. B.A. 1973, Carleton College; B.S. 1977, University of Iowa; Ph.D. 1983, University of Rochester School of Medicine and Dentistry

Breslow, Esther M., Professor of Biochemistry. B.S. 1953, Cornell University; M.S. 1955, Ph.D. 1959, New York University

Brooks, Dana C., Professor of Cell Biology and Anatomy. B.E.E. 1949, M.D. 1957, Cornell University Medical College

Brown, Anthony M.C., Assistant Professor of Cell Biology and Anatomy. Assistant Professor of Cell Biology and Anatomy in Microbiology. B.A. 1977, M.A. 1979, University of Cambridge (United Kingdom); Ph.D. 1981, University of Edinburgh (United Kingdom)

Bullough, Peter, Professor of Pathology. M.D. 1956, Liverpool University (United Kingdom)

Caudy, Michael, Assistant Professor of Cell Biology and Anatomy. Ph.D. 1985, University of California, Berkeley

Chaganti, Raju S., Professor of Cell Biology and Genetics in Pathology. B.S. 1954, M.S. 1955, Andhra University (India); Ph.D. 1964, Harvard University

Chan, Walter W. Y., Professor of Pharmacology. B.A. 1956, University of Wisconsin; Ph.D. 1961, Columbia University

Chao, Moses V., Professor of Cell Biology and Anatomy. Professor of Cell Biology and Anatomy in Medicine. B.A. 1973, Pomona College; Ph.D. 1980, University of California at Los Angeles

Chiorazzi, Nicholas, Professor of Medicine. B.A. 1966, College of the Holy Cross; M.D. 1970, Georgetown University School of Medicine

Chou, Ting-Chao, Professor of Molecular Pharmacology and Therapeutics. B.S. 1961, Kaohsiung Medical College (Taiwan); M.S. 1965, National Taiwan University; Ph.D. 1970, Yale University

Citi, Sandra, Assistant Professor of Cell Biology and Anatomy. M.D. 1989, University of Florence (Italy); Ph.D. 1986, Cambridge University (United Kingdom)

Cohen, Jacques, Associate Professor of Embryology in Obstetrics and Gynecology. B.Sc. 1974, State University of Leiden (The Netherlands); M.Sc. 1978, Ph.D. 1982, Erasmus University (The Netherlands)

Cooper, Arthur J. L., Research Professor of Biochemistry. Research Professor of Biochemistry in Neuroscience. B.Sc. 1967, M.Sc. 1969, University of London (United Kingdom); Ph.D. 1974, Cornell University Graduate School of Medical Sciences

Darnell, Robert B., Assistant Professor of Neurology and Neuroscience. B.A. 1979, Columbia University; M.D., Ph.D. 1985, Washington University School of Medicine

DeLotto, Robert, Assistant Professor of Molecular Biology. B.A. 1976, University of Pennsylvania; Ph.D. 1983, Princeton University

Deutsch, Paul, Assistant Professor of Medicine. A.B. 1975, Harvard College; M.D., Ph.D., 1982, Albert Einstein College of Medicine

Donner, David B., Associate Professor of Cell Biology and Genetics. B.A. 1966, Queens College of the City University of New York; Ph.D. 1972, Rensselaer Polytechnic Institute

Dorsett, Dale, Assistant Professor of Molecular Biology. B.A. 1976, Wabash College; Ph.D. 1980, University of Tennessee Oak Ridge Graduate School of Biomedical Sciences

Dreyfus, Cheryl F., Adjunct Research Associate Professor of Neuroscience (Robert Wood Johnson Medical School). Assistant Professor of Cell Biology and Anatomy. B.S. 1967, University of Vermont; M.S. 1969, Ph.D. 1976, Cornell University Graduate School of Medical Sciences

Duch, Daniel N.S., Assistant Professor of Physiology in Anesthesiology. Assistant Professor of Physiology and Biophysics. B.A. 1974, New York University; M.S. 1977, Colorado State University; Ph.D. 1986, University of Colorado Health Sciences Center

Dupont, Bo, Professor of Immunology. M.D. 1966, University of Arhus (Denmark)

Edelson, Paul, Associate Professor of Pediatrics. Associate Professor of Pediatrics in Microbiology. A.B. 1964, University of Rochester; M.D. 1969, State University of New York, Downstate Medical Center, Brooklyn, New York

Ellis, John T., The David D. Thompson Professor of Pathology. B.A. 1942, University of Texas; M.D. 1945, Northwestern University

Fairclough, Gordon F., Associate Professor of Clinical Biochemistry. Associate Professor of Clinical Biochemistry in Pathology. B.A. 1960, Ph.D. 1966, Yale University

Falck-Pedersen, Erik, Assistant Professor of Microbiology. B.A. 1976, North Central College; Ph.D. 1982, University of Illinois

Felsen, Diane, Associate Research Professor of Pharmacology in Surgery. B.A. 1974, Queens College of the City University of New York; Ph.D. 1979, Mt. Sinai School of Medicine

Fischman, Donald A., The Harvey Klein Professor of Biomedical Sciences. Professor of Cell Biology and Anatomy. A.B. 1957, Kenyon College; M.D. 1961, Cornell University Medical College

Freedman, Leonard, Assistant Professor of Cell Biology and Genetics. B.A. 1980, Kalamazoo College; M.S. 1982, Ph.D. 1985, University of Rochester

Furneaux, Henry M., Assistant Professor of Molecular Pharmacology and Therapeutics. Assistant Professor of Molecular Biology in Neuroscience. B.Sc. 1975, Ph.D. 1978, University of Aberdeen

Gardner, Daniel, Professor of Physiology and Biophysics. Professor of Physiology and Biophysics in Neuroscience. A.B. 1966, Columbia College; Ph.D. 1971, New York University

Gass, Jerald D., Associate Professor of Clinical Biochemistry. B.S. 1957, University of Oklahoma; A.M. 1962, Harvard University; Ph.D. 1969, Cornell University Graduate School of Medical Sciences

Gelbard, Allan S., Associate Professor of Molecular Pharmacology and Therapeutics. B.S. 1955, Brooklyn College of the City University of New York; M.S. 1956, University of Massachusetts; Ph.D. 1972, University of Wisconsin

German, James L. III, Clinical Professor of Pediatrics. B.S. 1945, Louisiana Polytechnic Institute; M.D. 1949, Southwestern Medical College

Gershengorn, Marvin C., The Abby Rockefeller Mauzé Distinguished Professor of Endocrinology in Medicine. Professor of Medicine in Physiology and Biophysics. B.S. 1967, City College of the City University of New York; M.D. 1971, New York University School of Medicine

Gibbs, James G. Jr., Professor of Psychiatry. B.S. 1960, Trinity College; M.D. 1964, Medical College of South Carolina

Gibson, Gary E., Professor of Neuroscience. B.S. 1968, University of Wyoming; Ph.D. 1973, Cornell University

Gilboa, Eli, Associate Professor of Molecular Biology. B.Sc. 1971, M.Sc. 1973, Hebrew University, Jerusalem; Ph.D. 1977, Weizmann Institute of Science (Israel)

Goldman, Steven A., Assistant Professor of Neurology and Neuroscience. B.A. 1978, University of Pennsylvania; M.D. 1984, Cornell University Medical College; Ph.D. 1983, The Rockefeller University

Goldstein, Jack, Adjunct Associate Professor of Biochemistry. B.A. 1952, Brooklyn College of the City University of New York; M.N.S. 1957, Ph.D. 1959, Cornell University

Grafstein, Bernice, The Vincent and Brook Astor Distinguished Professor of Neuroscience. Professor of Physiology and Biophysics. B.A. 1951, University of Toronto (Canada); Ph.D. 1954, McGill University (Canada)

Greif, Roger L., Professor Emeritus of Physiology and Biophysics. B.S. 1937, Haverford College; M.D. 1941, Johns Hopkins University

Griffith, Owen W., Professor of Biochemistry. B.A. 1968, University of California at Berkeley; Ph.D. 1976, The Rockefeller University

Gross, Steven S., Assistant Professor of Pharmacology. B.S. 1974, Brooklyn College of the City University of New York; M.P.H. 1979, Ph.D. 1982, Mt. Sinai School of Medicine

Gudas, Lorraine J., The Revlon Pharmaceutical Professor of Pharmacology and Toxicology. Professor of Pharmacology. B.A. 1970, Smith College; Ph.D. 1975, Princeton University

Hackett, Neil R., Assistant Professor of Microbiology. B.Sc. 1978, University of Edinburgh (United Kingdom); Ph.D. 1982, University of British Columbia (Canada)

Hajjar, David P., Professor of Pathology. Associate Professor of Biochemistry. B.A. 1974, American International College; M.S. 1977, Ph.D. 1978, University of New Hampshire

Hajjar, Katherine A., Associate Professor of Pediatrics. Associate Professor of Pediatrics in Medicine. A.B. 1974, Smith College; M.D. 1978, Johns Hopkins University School of Medicine

Hämmerling, Ulrich, Professor of Immunology. Diplom 1961, Universität Freiburg (Germany); Ph.D. 1965, Max Planck Institut für Immunobiologie (Germany)

Hartl, Franz-Ulrich, Associate Professor of Cell Biology and Genetics. M.D. 1985, University of Heidelberg (Germany)

Haschemeyer, Rudy H., Professor of Biochemistry. B.A. 1952, Carthage College; Ph.D. 1957, University of Illinois

Hayward, William S., Professor of Molecular Biology. B.A. 1964, University of California, Riverside; Ph.D. 1969, University of California, San Diego

Holloman, William K., Professor of Microbiology. B.S. 1967, University of Texas; Ph.D. 1971, University of California, Berkeley

Horecker, Bernard L., Dean, Professor Emeritus of Biochemistry. B.S. 1936, Ph.D. 1939, University of Chicago

Houghton, Alan, Associate Professor of Immunology. Associate Professor of Immunology in Medicine. B.A. 1970, Stanford University; M.D. 1974, University of Connecticut

Hurwitz, Jerard, American Cancer Society Research Professor. Professor of Molecular Biology. B.A. 1949, Indiana University; Ph.D. 1953, Western Reserve University

Hutchison, Dorris J., Professor Emeritus of Cell Biology and Genetics. B.S. 1940, Western Kentucky State College; M.S. 1943, University of Kentucky; Ph.D. 1949, Rutgers University

Inturrisi, Charles E., Professor of Pharmacology. B.S. 1962, University of Connecticut; M.S. 1965, Ph.D. 1967, Tulane University

Jack, Joseph R., Assistant Professor of Molecular Biology. B.A. 1972, Vanderbilt University; Ph.D. 1978, University of Texas

Jaffe, Eric, Professor of Medicine. M.D. 1966, State University of New York, Downstate Medical Center

Jasin, Maria, Assistant Professor of Cell Biology and Genetics. B.S. 1978, Florida Atlantic University; Ph.D. 1984, Massachusetts Institute of Technology

Joh, Tong Hyub, Professor of Neuroscience. B.S. 1953, Seoul National University (Korea); Ph.D. 1971, New York University

Kim, Kwang-Jin, Assistant Professor of Medicine. Assistant Professor of Physiology and Biophysics. B.S.E.E. 1971, M.S.E.E. 1973, Seoul National University (Korea); Ph.D. 1980, University of Pennsylvania

Klein, Irwin L., Professor of Medicine. B.A. 1969, University of Pennsylvania; M.D. 1973, New York University School of Medicine

Koutcher, Jason A., Associate Professor of Physics in Radiology. B.S. 1972, Massachusetts Institute of Technology; M.D., Ph.D. 1979, State University of New York Health Science Center at Brooklyn

Lacy, Elizabeth, Associate Professor of Molecular Biology. B.A. 1974, University of Pennsylvania; Ph.D. 1980, California Institute of Technology

Lai, Eseng, Assistant Professor of Cell Biology and Genetics. B.A. 1977, Yale University; M.D., Ph.D. 1983, Albert Einstein College of Medicine

Laughlin, John S., Professor of Molecular Pharmacology and Therapeutics. A.B. 1940, Willamette University; Ph.D. 1947, University of Illinois

Lee, Chin Ok, Professor of Physiology and Biophysics. M.S. 1967, Seoul National University (Korea); Ph.D. 1973, Indiana University School of Medicine

Lee, Janet S., Associate Professor of Immunology. B.A. 1972, University of Minnesota; M.S. 1974, University of Wisconsin; Ph.D. 1979, University of California at San Francisco

Levi, Roberto, Professor of Pharmacology. M.D. 1960, University of Florence (Italy)

Ling, C. Clifton, Professor of Molecular Pharmacology and Therapeutics. Professor of Physiology in Radiology. B.S. 1965, Oregon State University; Ph.D. 1971, University of Washington

Lipkin, Martin, Professor of Medicine. A.B. 1946, M.D. 1950, New York University

Lloyd, Kenneth O., Professor of Immunology. Ph.D. 1960, University of College of North Wales (United Kingdom)

Lusky, Monika, Assistant Professor of Microbiology. B.A. 1973, M.A. 1975, M.S. 1977, Ph.D. 1980, Albert-Ludwigs University, Freiberg (Germany)

Lustig, Arthur J., Assistant Professor of Molecular Biology. B.A. 1975, Ph.D. 1981, The University of Chicago

Maack, Thomas, Professor of Physiology and Biophysics. M.D. 1962, University of São Paulo (Brazil)

MacLeish, Peter R., Professor of Physiology in Ophthalmology. Professor of Physiology and Biophysics. B.E.Sc. 1969, University of Western Ontario (Canada); Ph.D. 1976, Harvard University

Marians, Kenneth J., Professor of Molecular Biology. B.S. 1972, Polytechnic Institute of Brooklyn; Ph.D. 1976, Cornell University

Marks, Paul A., Professor of Cell Biology and Genetics. Professor of Medicine. A.B. 1945, Columbia University; M.D. 1949, College of Physicians and Surgeons, Columbia University

Massagué, Joan, Howard Hughes Medical Institute Investigator. Professor of Cell Biology and Genetics. Licenciado en Farmacia 1975, Graduado en Farmacia 1975, Doctor en Farmacia 1978, University of Barcelona (Spain)

Meeley, Mary P., Assistant Professor of Neuroscience. B.S. 1974, Merrimack College; Ph.D. 1980, University of Maryland

Meister, Alton, The Israel Rogosin Professor of Biochemistry. B.S. 1942, Harvard University; M.D. 1945, Cornell University Medical College

Mendelsohn, John, Professor of Molecular Pharmacology and Therapeutics. Professor of Medicine. B.A. 1958, Harvard College; M.D. 1963, Harvard Medical College

Milner, Theresa A., Assistant Professor of Neuroscience. B.S. 1978, University of California, Irvine; Ph.D. 1982, University of California, San Diego

Minick, C. Richard, Professor of Pathology. B.S. 1957, University of Wyoming; M.D. 1960, Cornell University Medical College

Moore, Malcolm A. S., Professor of Cell Biology and Genetics. M.B. 1963, B.A. 1964, D. Phil. 1967, M.A. 1970, Oxford University (United Kingdom)

Muller-Eberhard, Ursula, Professor of Pediatrics. Professor of Pharmacology. M.D. 1953, University of Göttingen (Germany)

Murray, Henry W., Professor of Medicine. B.A. 1968, Cornell University; M.D. 1972, Cornell University Medical College

Nachman, Ralph L., The Mark W. Pasmantier Professor of Medicine. A.B. 1953, M.D. 1956, Vanderbilt University

Nathan, Carl F., The Stanton Griffis Distinguished Professor of Medicine. B.A. 1967, Harvard University; M.D. 1972, Harvard Medical School.

Neff, Norma, Assistant Professor of Molecular Biology. B.A. 1974, Rice University; Ph.D. 1978, University of California, Berkeley

Nikolic-Zugic, Janko, Assistant Professor of Immunology, M.D. 1984, Belgrade University Medical School (Yugoslavia)

Novogrodsky, Abraham, Professor of Biochemistry. Professor of Biochemistry in Medicine. M.D. 1960, Hebrew University Medical School, Jerusalem; Ph.D. 1974, Weizmann Institute of Science (Israel)

O'Donnell, Michael E., Associate Professor of Microbiology. B.S. 1975, University of Portland; Ph.D. 1982, University of Michigan

Oettgen, Herbert F., Professor of Immunology. Professor of Medicine. M.D. 1951, University of Cologne (Germany)

Okamoto, Michiko, Professor of Pharmacology. Professor of Pharmacology in Anesthesiology. B.S. 1954, Tokyo College of Pharmacy (Japan); M.S. 1957, Purdue University; Ph.D. 1964, Cornell University Graduate School of Medical Sciences

Old, Lloyd J., Professor of Immunology. B.A. 1955, M.D. 1958, University of California

O'Leary, William M., Professor of Microbiology. B.S. 1952, M.S. 1953, Ph.D. 1957, University of Pittsburgh

O'Reilly, Richard J., Professor of Immunology. Professor of Pediatrics. A.B. 1964, College of the Holy Cross; M.D. 1968, University of Rochester

Osley, Mary Ann, Associate Professor of Molecular Biology. B.A. 1967, Wheaton College; Ph.D. 1973, Yale University

Palmer, Lawrence G., Professor of Physiology and Biophysics. B.A. 1970, Swarthmore College; Ph.D. 1976, University of Pennsylvania

Pardee, Joel D., Associate Professor of Cell Biology and Anatomy. B.S. 1973, Colorado State University; Ph.D. 1978, Stanford University

Pasternak, Gavril W., Professor of Molecular Pharmacology and Therapeutics. Professor of Pharmacology. Professor of Neurology and Neuroscience. B.A. 1969, M.D. 1973, Ph.D. 1974, Johns Hopkins University

Petito, Carol K., Professor of Pathology. B.S. 1963, Jackson College; M.D. 1967, Columbia University

Pickel, Virginia M., Professor of Neuroscience. B.S. 1965, M.S. 1967, University of Tennessee; Ph.D. 1970, Vanderbilt University

Pickering, Thomas G., Professor of Medicine. B.A. 1962, M.A. 1968, Cambridge University (United Kingdom); Ph.D. 1970, Oxford University (United Kingdom)

Plum, Fred, The Anne Parrish Titzell Professor of Neurology. B.A. 1944, Dartmouth College; M.D. 1947, Cornell University Medical College

Posner, Jerome B., Professor of Molecular Pharmacology and Therapeutics. Professor of Neurology and Neuroscience. B.S. 1951, University of Washington; M.D. 1955, University of Washington School of Medicine

Posnett, David Neil, Associate Professor of Medicine. M.D. 1977, University of Geneva (Switzerland)

Prince, Alfred M., Clinical Associate Professor of Pathology. A.B. 1949, Yale University; M.A. 1951, Columbia University; M.D. 1955, Western Reserve University

Prochaska, Hans J., Assistant Professor of Molecular Pharmacology and Therapeutics. B.S.Ch.E. 1981, Rutgers University; M.D., Ph.D. 1986, Johns Hopkins University School of Medicine

Pulsinelli, William Anthony, Professor of Neurology and Neuroscience. B.S. 1965, Villanova University; Ph.D. 1970, M.D. 1973, University of Utah College of Medicine

Quimby, Fred, Associate Professor of Pathology. V.D.M. 1970, University of Pennsylvania School of Veterinary Medicine; Ph.D. 1974, University of Pennsylvania Graduate School of Arts and Sciences

Rabkin, Samuel D., Assistant Professor of Molecular Biology. B.Sc. 1976, University of Toronto (Canada); M.Sc. 1978, Hebrew University of Jerusalem (Israel); Ph.D. 1983, University of Chicago

Rachele, Julian R., Professor Emeritus of Biochemistry. B.A. 1934, M.S. 1935, Ph.D. 1939, New York University

Ravetch, Jeffrey A., Professor of Molecular Biology. B.S. 1973, Yale University; Ph.D. 1978, The Rockefeller University; M.D. 1979, Cornell University Medical College

Rayson, Barbara, Associate Professor of Physiology and Biophysics. Associate Professor of Physiology in Medicine. B.Sc. 1972, Ph.D. 1976, University of Melbourne (Australia)

Reeves, John P., Adjunct Associate Professor of Physiology and Biophysics (Roche Institute of Molecular Biology). B.S. 1964, Juniata College; Ph.D. 1969, Massachusetts Institute of Technology

Reidenberg, Marcus M., Professor of Pharmacology. Professor of Medicine. M.D. 1958, Temple University School of Medicine

Reis, Donald J., The George C. Cotzias Distinguished Professor of Neurology. Professor of Neurology in Psychiatry. A.B. 1953, M.D. 1956, Cornell University Medical College

Resh, Marilyn D., Associate Professor of Cell Biology and Genetics. B.A. 1977, Princeton University; Ph.D. 1982, Harvard University

Rettig, Wolfgang, Assistant Professor of Immunology. M.D. 1979, Ph.D. 1983, Freie Universität Berlin (Germany)

Rifkind, Arleen B., Professor of Pharmacology. Associate Professor of Medicine. B.A. 1960, Bryn Mawr College; M.D. 1964, New York University

Rifkind, Richard A., Director, Sloan-Kettering Division. Professor of Cell Biology and Genetics. B.S. 1951, Yale University; M.D. 1955, Columbia University

Riker, Walter F., Jr., The Revlon Pharmaceutical Professor Emeritus of Pharmacology and Toxicology. Professor Emeritus of Pharmacology. B.S. 1939, Columbia University; M.D. 1943, Cornell University Medical College

Robertson, Hugh D., Associate Professor of Biochemistry. B.A. 1964, Harvard College; Ph.D. 1969, The Rockefeller University

Rodriguez-Boulan, Enrique, The Joseph C. Hinsey Professor of Cell Biology and Anatomy. B.A. 1963, National College of Buenos Aires; M.D. 1970, University of Buenos Aires (Argentina)

Roepe, Paul D., Assistant Professor of Molecular Pharmacology and Therapeutics. B.A. 1982, M.A. 1984, Ph.D. 1987, Boston University

Rothman, James E., Professor of Cell Biology and Genetics. B.A. 1971, Yale College; Ph.D. 1976, Harvard Medical School

Rottenberg, David A., Adjunct Professor of Neuroscience and Neurology (University of Minnesota). B.A. 1963, University of Michigan; M.Sc. 1967, University of Cambridge (United Kingdom); M.D. 1969, Harvard University

Rubin, Albert L., Professor of Biochemistry. Professor of Surgery. Professor of Medicine. M.D. 1950, Cornell University Medical College

Ruggiero, David A., Associate Research Professor of Neuroscience. B.A. 1972, Queens College of the City University of New York; M.A. 1976, M. Phil. 1977, Ph.D. 1977, Columbia University

Russo, Carlo, Associate Professor of Medicine. M.D. 1977, University of Genova Medical School (Italy)

Sackin, Henry J., Associate Professor of Physiology and Biophysics. B.A., B.S. 1970, M.S. 1971, Brown University; Ph.D. 1978, Yale University

Saltiel, Alan R., Adjunct Assistant Professor (The Rockefeller University). A.B. 1975, Duke University; Ph.D. 1980, University of North Carolina

Santos-Buch, Charles A., Professor of Pathology. A.B. 1953, Harvard University; M.D. 1957, Cornell University Medical College

Saxena, Brij B., Professor of Endocrinology in Obstetrics and Gynecology. Ph.D. 1954, University of Lucknow (India); D.Sc. 1957, University of Münster (Germany); Ph.D. 1961, University of Wisconsin

Scheinberg, David A., Assistant Professor of Molecular Pharmacology and Therapeutics. A.B. 1977, Cornell University; M.D., Ph.D. 1983, Johns Hopkins University School of Medicine

Schubert, Edward T., Associate Professor of Biochemistry in Clinical Pathology. Associate Professor of Clinical Biochemistry. Assistant Professor of Biochemistry in Pediatrics. B.S. 1949, M.S. 1952, Ph.D. 1959, Fordham University

Schwab, Rise, Assistant Professor of Immunology in Medicine. B.S. 1971, State University of New York at Stony Brook; Ph.D. 1981, Cornell University

Schwartz, Morton K., Professor of Molecular Pharmacology and Therapeutics. B.A. 1948, Lehigh University; Ph.D. 1952, Boston University

Scotto, Kathleen Weihs, Assistant Professor of Molecular Pharmacology and Therapeutics. B.S. 1977, St. John's University; Ph.D. 1983, Cornell University Graduate School of Medical Sciences

Sechzer, Jeri A., Associate Professor of Psychology in Psychiatry. B.S. 1956, New York University; M.A. 1961, Ph.D. 1962, University of Pennsylvania

Senterfit, Laurence B., Professor of Microbiology. Professor of Pathology. B.S. 1949, M.S. 1950, University of Florida; Sc.D. 1955, Johns Hopkins University

Sheffery, Michael B., Associate Professor of Molecular Biology. A.B. 1975, M.S. 1977, Ph.D. 1981, Princeton University

Shuman, Stewart, Assistant Professor of Molecular Biology. B.A. 1976, Wesleyan University; M.D., Ph.D. 1983, Albert Einstein College of Medicine

Silagi, Selma, Professor Emeritus of Genetics in Obstetrics and Gynecology. B.A. 1936, Hunter College of the City University of New York; M.A. 1938, Columbia University; Ph.D. 1961, Columbia University

Silverstein, Roy L., Assistant Professor of Medicine. B.S. 1975, Brown University; M.D. 1979, Emory University School of Medicine

Sirlin, Julio L., Professor of Cell Biology and Anatomy. Professor of Cell Biology in Obstetrics and Gynecology. D.Sc. 1953, University of Buenos Aires (Argentina)

Sirotnak, Francis M., Professor of Molecular Pharmacology and Therapeutics. B.S. 1950, University of Scranton; M.S. 1952, University of New Hampshire; Ph.D. 1954, University of Maryland

Siskind, Gregory W., Professor of Medicine. B.A. 1955, Cornell University; M.D. 1959, New York University

Smith, Gerard P., Professor of Psychiatry B.S. 1956, St. Joseph's College; M.D. 1960, University of Pennsylvania

Soffer, Richard L., Professor of Medicine. Professor of Biochemistry. B.A. 1954, Amherst College; M.D. 1958, Harvard University

Sonenberg, Martin, Professor of Cell Biology and Genetics. Professor of Medicine. B.S. 1941, University of Pennsylvania; M.D. 1944, Ph.D. 1952, New York University

Staiano-Coico, Lisa, Associate Professor of Microbiology in Surgery. B.S. 1976, Brooklyn College of the City University of New York; Ph.D. 1981, Cornell University Graduate School of Medical Sciences

Stenzel, Kurt H., Professor of Biochemistry. Professor of Surgery. Professor of Medicine. B.S. 1954, New York University; M.D. 1958, Cornell University Medical College

Stephenson, John L., Professor of Biomathematics in Physiology and Biophysics. B.A. 1943, Harvard University; M.D. 1949, University of Illinois

Sternberg, Stephen S., Professor of Molecular Pharmacology and Therapeutics. B.A. 1941, Colby College; M.D. 1944, New York University

Stokes, Peter E., Professor of Medicine. Professor of Psychiatry. B.S. 1948, Trinity College; M.D. 1952, Cornell University Medical College

Stutman, Osias, Professor of Immunology. B.A. 1950, Colegio Nacional Sarmiento (Argentina); M.D. 1957, Buenos Aires University Medical School (Argentina)

Sussdorf, Dieter H., Associate Dean, Associate Professor of Microbiology. B.A. 1952, University of Missouri; Ph.D. 1956, University of Chicago

Szeto, Hazel H., Associate Professor of Pharmacology. B.S. 1972, Indiana University; M.D. 1977, Cornell University Medical College; Ph.D. 1977, Cornell University Graduate School of Medical Sciences

Tate, Suresh S., Associate Professor of Biochemistry. B.Sc. 1958, M.Sc. 1960, University of Baroda (India); Ph.D. 1963, University of London (United Kingdom)

Tempst, Paul, Associate Professor of Molecular Biology. B.S. 1976, Ghent State University (Belgium); Ph.D. 1981, Ghent University (Belgium)

Townes-Anderson, Ellen, Associate Professor of Physiology and Biophysics. Associate Professor of Physiology in Ophthalmology. B.A. 1968, Connecticut College; M.A. 1971, University of California at Berkeley; Ph.D. 1980, Boston University School of Medicine

Traktman, Paula, Associate Professor of Cell Biology and Anatomy. Associate Professor of Cell Biology and Anatomy in Microbiology. A.B. 1974, Radcliffe College, Harvard University; Ph.D. 1981, Massachusetts Institute of Technology

Udenfriend, Sidney, Adjunct Professor of Biochemistry. B.S. 1939, City College of the City University of New York; M.S. 1942, Ph.D. 1948, New York University

Victor, Jonathan D., Professor of Neurology and Neuroscience. B.A. 1973, Harvard University; Ph.D. 1979, The Rockefeller University; M.D. 1980, Cornell University Medical College

Volpe, Bruce T., Associate Professor of Neurology and Neuroscience. B.S. 1969, Yale College; M.D. 1973, Yale University School of Medicine

Wagner, John A., Professor of Neurology and Neuroscience. B.S. 1970, Loras College; Ph.D. 1975, Princeton University

Wahlestedt, Claes R., Assistant Professor of Neuroscience. M.D. 1984, Ph.D. 1987, University of Lund (Sweden)

Watanabe, Kyoichi A., Professor of Molecular Pharmacology and Therapeutics. Ph.D. 1963, Hokkaido University (Japan)

Weinstein, Alan M., Associate Professor of Physiology and Biophysics. Associate Professor of Medicine. A.B. 1971, Princeton University; M.D. 1975, Harvard University

Weksler, Babette B., Professor of Medicine. B.A. 1958, Swarthmore College; M.D. 1963, Columbia University

Weksler, Marc E., The Irving Sherwood Wright Professor of Geriatrics in Medicine. B.A. 1958, Swarthmore College; M.D. 1962, Columbia University

Wellner, Daniel, Associate Professor of Biochemistry. A.B. 1956, Harvard University; Ph.D. 1961, Tufts University

White, Perrin C., Associate Professor of Pediatrics. A.B. 1972, Harvard University; M.D. 1976, Harvard Medical School

Wiedmann, Martin, Assistant Professor of Cell Biology and Genetics. Diplom 1975, University of Greifswald (Germany); Ph.D. 1979, University of Potsdam (Germany)

Windhager, Erich E., The Maxwell M. Upson Professor of Physiology and Biophysics. M.D. 1954, University of Vienna (Austria)

Yang, Soo Young, Associate Professor of Immunology. M.S. 1972, Minnesota State University; Ph.D. 1981, New York University

Zakim, David, The Vincent Astor Distinguished Professor of Medicine. B.A. 1956, Cornell University; M.D. 1961, State University of New York Downstate Medical Center

Degree Recipients 1990–91

Doctors of Philosophy

Barnhart, Kerry M., B.S. 1983, M.S. 1985, University of Arizona; Molecular Biology, Professor Michael Sheffery. Thesis: "Identification and Characterization of Multiple Murine Erythroid Transcription Factors."

Bauchwitz, Robert P., B.A. 1982, Harvard University; Molecular Biology, Professor William Holloman. Thesis: "Cloning and Characterization of the Rec2 Gene of *Ustilago Maydis*."

Bayer, Virginia E., B.A./B.S. 1981, University of California; Neuroscience, Professor Virginia M. Pickel. Thesis: "Mesocorticolimbic Dopamine Circuitry: An Ultrastructural Analysis."

Berger, Scott B., B.A. 1983, Emory University; Neuroscience, Professor Donald J. Reis. Thesis: "Three-Dimensional, Volumetric Analysis of Regions-of-Difference: Application to Studies of Rat Brain."

Chiu, Chang-Fang, M.D. 1980, Taipei Medical College, China; Cell Biology and Genetics, Professor Magdalena Eisinger. Thesis: "The Role of Protein Kinase C in Growth Regulation of Human Melanoma Cells."

Dicker, Adam P., B.A. 1984, Columbia University; Pharmacology, Professor Joseph R. Bertino. Thesis: "Molecular Characterization of Mutations in the Dihydrofolate Reductase Gene That Result in Methotrexate Resistance."

Escandon, Enrique M., B.S. 1985, Universidad Nacional Autonoma de Mexico; Cell Biology and Genetics, Professor Moses V. Chao. Thesis: "Regulation and Characterization of the NGF Receptor During Central Nervous System Development."

Febbraio, Maria, B.S. 1982, Fordham University; Microbiology, Immunology, and Pathology, Professor Roy L. Silverstein. Thesis: "Identification and Characterization of an Activation-Dependent Platelet Glycoprotein, LAMP-1."

Fotheringham, R. Scott, B.Sc. 1985, University of Guelph (Canada); Molecular Biology, Professor William Holloman. Thesis: "Genetics Control of Mitotic Recombination in *Ustilago Maydis*."

Gundersen, Doris I., B.A. 1977, Clark University; Cell Biology and Genetics, Professor Enrique Rodriguez-Boulan. Thesis: "Reversed Polarity in Retinal Pigment Epithelium."

Kim, Chul Geun, B.S. 1981, Han Yang University; M.S. 1983, Seoul National University; Molecular Biology, Professor Michael Sheffery. Thesis: "The Transcriptional Regulation of α-globin Gene Expression: Purification and Biochemical Characterization of Multiple Transcription Factors."

Lisanti, Michael P., B.A. 1985, New York University; Cell Biology and Genetics, Professor Enrique Rodriguez-Boulan. Thesis: "Glycophospholipid Membrane Anchoring Functions as an Apical Targeting Signal in Polarized Epithelial Cells."

Maher, Kevin J., B.S. 1987, Manhattan College; Microbiology, Immunology, and Pathology, Professor Carl G. Becker. Thesis: "Tobacco Glycoprotein Mediated Alterations of Plasmin(ogen) Function."

Maki, Robert G., B.A. 1985, Northwestern University; Immunology, Professor Lloyd J. Old. Thesis: "The Human Homologue of the Mouse Tumor Rejection Antigen gp96."

Mandell, James W., A.B. 1984, Cornell University; Neuroscience, Professor Ellen Townes-Anderson. Thesis: "Studies on Retinal Synapses: Molecular Heterogeneity and Structural Plasticity."

Marino, Michael W., B.A. 1983, Skidmore College; M.S. 1985, University of Texas; Cell Biology and Genetics, Professor David B. Donner. Thesis: "Phosphorylation of the Protooncogene Product eIF-4E is a Commun Cellular Response to Tumor Necrosis Factor."

Nussenzveig, Daniel R., M.D. 1980, University of São Paulo; Physiology and Biophysics, Professor Thomas Maack. Thesis: "Cellular Mechanisms of the Clearance Function of Type c Receptors of Atrial Natriuretic Factor."

Parada, Camilo A., B.S. 1978, Catholic University of Valparaiso, Chile; Molecular Biology, Professor Kenneth J. Marians. Thesis: "Role of Transcriptional Activation in Alternate Pathways of Initiation of pBR 322 DNA Replication *in vitro*."

Patil, Nila J., B.A. 1980, University of Buffalo; Cell Biology and Genetics, Professor Moses V. Chao. Thesis: "Expression of Nerve Growth Factor Receptor in Transgenic Mice."

Pearse, Roger N., B.A. 1977, Dartmouth College; Microbiology, Immunology, and Pathology, Professor Carl G. Becker. Thesis: "Characterization of a Bradykinin Receptor."

Pincus, David W., B.S. 1985, Yale University; Neuroscience, Professor Ira B. Black. Thesis: "Neuropeptide Regulation of Neuronal Development."

Russell, David S., B.A. 1982, Oberlin College; Molecular Biology, Professor Ora M. Rosen. Thesis: "Studies on the Human Insulin Factor."

Sgouros, George, B.S. 1984, Columbia University; Physiology and Biophysics, Professor Rodney E. Bigler. Thesis: "The Effects of Ionizing Radiation on Brain Metabolism of Glucose: Radiation-Induced Activation of the Pentose Phosphate Pathway."

Solomon, David H., A.B. 1982, Oberlin College (Canada); Immunology, Professor Yvon Cayre. Thesis: "Regulation of Fructose-1,6-Bisphosphatase Expression During Monocytic Differentiation."

Sordillo, Emilia Mia, A.B. 1976, Harvard University; M.D. 1980 Cornell University Medical College; Immunology, Professor Robert A. Good. Thesis: "Evolution of Severe Combined Immunodeficiency in Mice Treated with 2′ Deoxycoformycin."

Straub, Richard E., B.A. 1982, New College; Cell Biology and Genetics, Professor Marvin C. Gershengorn. Thesis: "Expression Cloning and Characterization of a cDNA Encoding the Mouse Pituitary Thyrotropin-Releasing Hormone Receptor."

Sullenger, Bruce A., B.S. 1986, Colgate University; Molecular Biology, Professor Eli Gilboa. Thesis: "Development of a tRNA Based Transcription System to Render Cells Resistant to Viral Replication."

Tan, Jimmy C., B.S. 1985, Ateneo de Manila, Philippines; Molecular Biology, Professor Peter Besmer. Thesis: "Molecular Basis of Murine White-Spotting (W) Phenotypes: Mutations in the C-Kit Proto-Oncogene."

Wong, Gwendolyn T., B.S. 1984, McMaster University (Canada); Molecular Biology, Professor Elizabeth Lacy. Thesis: "Studies on the Structure and Expression of the Human CD4 Gene."

Wu, Kai-Yuan, B.A. 1983, New York University; Cell Biology and Genetics, Professor Martin Sonenberg. Thesis: "*In Vitro* Study of Bovine Growth Hormone Fragments—Dissociation of Growth Hormone Actions."

Yan, Hai, B.S. 1982, Nanjing University, P. R. China; Cell Biology and Genetics, Professor Moses V. Chao. Thesis: "Functional Analysis of Human p75 Nerve Growth Factor Receptor."

Masters of Science

Cuerdon, Elizabeth E., B.S. 1985, Siena College; Microbiology, Immunology, and Pathology, Professor Constance Davis Rothermel. Thesis: "*Chlamydia trachomatis* Induces Human Peripheral Blood Mononuclear Cells to Proliferate and Produce Interleukin 2 and Gamma-Interferon."

Hodgins, Gregory W. L., B.Sc. 1985, University of Toronto (Canada); Molecular Biology, Professor William Holloman. Thesis: "Identification of an ATP-independent Strand Transfer Activity in Human Cells."

Pitarresi, Tina, B.A. 1983, Rutgers University; Physiology and Biophysics, Professor Jean E. Sealey. Thesis: "Reversible Cryoactivation of Recombinant Human Prorenin."

Students 1991–92

Candidates for the Degree of Doctor of Philosophy

Entering Students

Brown, George P. (Neuroscience). B.S. 1990, Fordham University. Worcester, Massachusetts

Chen, Bihua (Molecular Biology). B.S. 1990, Fudan University (China). Zhejiang, P. R. China

Deng, Liang (Cell Biology and Genetics). B.S. 1991, University of Rochester. Huzhou City, P. R. China

DiBenedetto, Cheryl (Immunology). B.A. 1991, New York University. Teaneck, New Jersey

Egan, David A. (Neuroscience). B.Sc. 1991, University of Limerick (Ireland). Limerick, Ireland

Espinoza, Kathryn G. (Neuroscience). B.S. 1989, Hofstra Univesity. Port Washington, New York

Fang, Linhua (Molecular Biology). B.S. 1985, Zhejiang Medical University (China); M.S. 1989, Peking Union Medical College (China). Zhejiang, P. R. China

Gibbs, Emma E. (Molecular Biology). B.Sc. 1988, M.Sc. 1991, University of Auckland (New Zealand). Auckland, New Zealand

Goriely, Anne E. (Cell Biology and Genetics). Ingénieur Agronomie 1988, Université Libre de Bruxelles (Belgium). Watermael-Boitsfort, Belgium

Grills, George S. (Cell Biology and Genetics). B.S. 1989, Columbia University. New York, New York

Hamilton, Sarah K. (Immunology). B.S. 1991, Bates College. Royal Oak, Michigan

Hatini, Victor (Molecular Biology). B.A. 1989, Hebrew University of Jerusalem (Israel); M.Sc. 1991, Weizmann Institute of Science (Israel). Jerusalem, Israel

Jin, Fen Yu (Immunology). B.M. 1990, Beijing Medical University (China). Beijing, P. R. China

Lemon, Bryan D. (Molecular Biology). B.S. 1991, University of Delaware. Havre de Grace, Maryland

Li, Bibo (Physiology and Biophysics). B.S. 1990, Peking University (China). Beijing, P. R. China

Li, Tao (Molecular Biology). B.S. 1988, Beijing Normal University (China); M.S. 1991, Institute of Microbiology, Academia Sinica (China). Hunan Province, P. R. China

Liu, Jing (Biochemistry). B.S. 1987, Peking University (China). Tianjin, P. R. China

Liu, Ke (Molecular Biology). B.M. 1984, Henan Medical University (China); M.M. 1988, National Institute for the Control of Pharmaceutical and Biological Products (China). Neixiang, P. R. China

MacMicking, John (Immunology). B.S. 1991, Australian National University. Temora, Australia

Molano, Alberto (Immunology). M.D. 1988, Colegio Mayor de Nuestra Señora del Rosario, School of Medicine (Colombia). Bogotá, Colombia

Netzer, William J. (Immunology). B.S. 1971, Brooklyn College, Brooklyn, New York

Ng, Yik-Bing Jenny (Molecular Biology). B. Sc. 1987, University of Calgary (Canada). Hong Kong

Niu, Hongwu (Molecular Biology). B.S. 1988, M.A. 1991, Peking University (China). Shanghai, P. R. China

Oh, Jooyeon (Molecular Biology). B.S. 1991, California State Polytechnic University, Seoul, Korea

Polyak, Kornelia (Molecular Biology). M.D. 1991, Albert Szent-Györgyi Medical University (Hungary). Jaszbereny, Hungary

Rao, Prakash K. (Immunology). B.A. 1991, University of California, Santa Barbara. Gobichettypalayam, India

Ryeom, Sandra W. (Cell Biology and Genetics). B.A. 1989, Wellesley College. Los Angeles, California

Sekiguchi, JoAnn M. (Molecular Biology). B.S., B.A. 1987, University of California, Davis. Ann Arbor, Michigan

Thio, Guene L. (Molecular Biology). B.A. 1991, University of Pennsylvania. Cleveland, Ohio

Todorov, Zlatko V. (Molecular Biology). B.S. 1991, Bucknell University. Plovdiv, Bulgaria

Tong, Youzhi (Pharmacology). B.S. 1984, M.S. 1988, Peking University (China). Shanghai, P. R. China

Tortorelli, Valeria (Immunology). B.S. 1990, Georgetown University. Taranto, Italy

Tsai, Jason (Physiology and Biophysics). B.S. 1991, Pennsylvania State University. Taiwan, Republic of China

Turner, Jennifer L. (Molecular Biology). B.S. 1991, William Smith College. Wilmington, Delaware

Vosseller, Keith A. (Molecular Biology). B.A. 1988, Miami University. Frankfurt, Germany

Wang, Shu (Molecular Biology). B.S. 1990, Nankai University (China). Changsha, P. R. China

Wang, Yan (Biochemstry). B.S. 1986, Peking University (China). Beijing, P. R. China

Weber, Lawrence W. (Pharmacology). B.S. 1991, Rensselaer Polytechnic Institute. Syracuse, New York

Weis, Frances M. B. (Cell Biology and Genetics). B.S. 1987, College of St. Elizabeth; M.Sc. 1991, University of Massachusetts Graduate School of Biomedical Sciences. Trenton, New Jersey

Xuan, Shouhong (Cell Biology and Genetics). B.S. 1985, Sichuan University (China). Kunming, P. R. China

Yan, Wei (Cell Biology and Genetics). B.S. 1987, Peking University (China). Xian, P. R. China

Yan, Yan (Physiology and Biophysics). B.S. 1991, Peking University (China). Wuhan City, P. R. China

Yao, Nina Ye-Hua (Molecular Biology). B.Sc. 1991, University of Toronto (Canada). Ottawa, Canada

Zhong, Fengming (Molecular Biology). B.M. 1984, M.M. 1990, Zhejiang Medical University (China). Tongxiang, Zhejiang, P. R. China

Zhou, Wenjun (Pharmacology). B.S. 1989, Fudan University (China). Hubei, P. R. China

Continuing Students

Abraham, Dicky G. (Biochemistry). M.S. 1987, Indian Institute of Technology. Kuwait City, Kuwait

Ahn, Jong C. (Molecular Biology). B.S. 1979, Seoul National University; M.S. 1981, Korea Advanced Institute of Science and Technology. Seoul, Korea

Alroy, Iris (Cell Biology and Genetics). B.S. 1989, Tel Aviv University. Tel Aviv, Israel

Altun, Zeynep F. (Neuroscience). M.D. 1985, Istanbul Faculty of Medicine, Trabzon, Turkey

[1]Arnold, James B. (Neuroscience). B.A. 1982, Columbia College. New York, New York

August, Avery (Immunology). B.A. 1987, University of California, Los Angeles. Belize City, Belize

Bannerji, Rajat (Molecular Biology). B.A. 1986, Cornell University. Durgapur, India

Bannish, Gregory (Immunology). B.S. 1990, University of Massachusetts, Amherst. Springfield, Massachusetts

Battleman, David (Cell Biology and Genetics). B.A. 1988, Johns Hopkins University. Queens, New York

Becker, Murray D. (Physiology and Biophysics). B.A. 1985, University of Chicago. Chicago, Illinois

Berg, Margaret (Cell Biology and Genetics). B.S. 1985, University of Illinois; M.S. 1987, Cornell University. Chicago, Illinois

Bisaha, Joseph G. (Cell Biology and Genetics). B.A. 1986, Rutgers University. Perth Amboy, New Jersey

Blum, Michele D. (Molecular Biology). B.A. 1986, Lafayette College. Philadelphia, Pennsylvania

Bosenberg, Marcus (Cell Biology and Genetics). B.A. 1976, Cornell University. Princeton, New Jersey

Bradley, Roger S. (Cell Biology and Genetics). B.A. 1984, Carroll College. Billings, Montana

[2]Brayton, Cory Flagg (Microbiology, Immunology, and Pathology). B.A. 1981, Williams College; D.V.M. 1985, New York State College of Veterinary Medicine. New York, New York

Brodsky, Marina (Pharmacology). First Degree 1984, Kalinin State University (USSR). Moscow, USSR

Brooks, David G. (Molecular Biology). B.A. 1982, University of Colorado; M.S. 1984, Michigan State University. Pontiac, Michigan

Buck, Regina (Immunology). B.A. 1988, Hunter College. Rottweil, Germany

Buckanovich, Ronald J. B.S. 1990, Cornell University. Buffalo, New York

Burris, Judith A. Cupp (Immunology). B.S., B.A. 1987, Missouri Southern State College. Joplin, Missouri

Chang, Shang-Yu (Molecular Biology). B.S. 1985, M.S. 1987, National Tsing-Hua University. Taipei, Taiwan, Republic of China

Chen, Benjamin Kuan. B.A.S. 1990, Stanford University. New York, New York

[2]Chen, Liu-Er (Neuroscience). B.M. 1984, Anhui Medical Unviersity, M.S. 1987, Shanghai Institute of Materia Medica. Anhui, P. R. China

Cheng, Jie (Neuroscience). B.M. 1988, Shanghai Medical University. Shanghai, P. R. China

Cheng, Peter (Pharmacology). B.A. 1986, Cornell University. M.S. 1988, Tufts University. Hsinchu, Taiwan, Republic of China

Cho, Hearn (Immunology) A.B. 1988, Princeton University. Las Vegas, Nevada

Cho, Jae-Young (Neuroscience). B.S. 1988, Pusan National University. Seoul, Korea

Cho, Sunghee (Neuroscience). B.S. 1979, Yonsei University. Jinhae, Korea

Chu, Tang-Yuan (Molecular Biology). M.D. 1983, National Defense Medical Center. Taipei, Taiwan, Republic of China

Circle, David A. (Biochemistry). B.S. 1990, University of Georgia. Marietta, Georgia

Claude, Alejandro (Molecular Biology). M.S. 1987, Universidad Catolica (Chile). Santiago, Chile

Cong, Peijie (Molecular Biology). B.S. 1984, The Fourth Army Medical College; M.S. 1987, Institute of Radiation Medicine. Shandong, P. R. China

Corradi, John P. (Neuroscience). B.S. 1987, Columbia University. Flushing, New York

Crombie, Andrea Rene (Molecular Biology). B.A. 1981, Goucher College. San Diego, California

de Bruin, Derik (Molecular Biology). B.S. 1986, Eastern New Mexico University. Bozeman, Montana

DiMartino, Jorge (Immunology). B.A. 1985, University of California, Berkeley. Rosario, Argentina

Ding, Xiao-Hong (Molecular Biology). B.S. 1984, Shanghai Medical University; M.S. 1988, Shanghai Institute of Materia Medica, Chinese Academy of Sciences. Hangzhou, P. R. China

Dovat, Siniša (Molecular Biology). M.D. 1988, University in Novi Sad Faculty of Medicine (Yugoslavia). Novi Sad, Yugoslavia

Du, Shan (Cell Biology and Genetics). B.S. 1984, M.S. 1987, Peking University. Chengdu, P. R. China

Dyall, Rubendra (Immunology). B.Sc., M.Sc. 1988, School of Medicine, University of Bordeaux II (France). Mauritius

Edwalds-Gilbert, Gretchen E. (Molecular Biology). B.A. 1982, Swarthmore College. Syracuse, New York.

Einarson, Margaret (Molecular Biology). B.S. 1988, Bates College. New York, New York

Eisenberg, Carol Ann (Cell Biology and Genetics). B.S., B.A. 1981, Cabrini College; M.S. 1983, Villanova University. Havertown, Pennsylvania

[1]Elliott, Robert (Neuroscience). A.B. 1983, University of California, Berkeley. Los Angeles, California

Erçikan, Emine A. B.S. 1986, M.S. 1988, University of Southwestern Louisiana. Nicosia, Cyprus

Ferguson, David (Molecular Biology). B.S. 1988, University of Rochester. New York, New York

Fernandez-Almonacid, Rafael (Molecular Biology). B.Sc. 1980, M.Sc. 1985, Universidad Austral De Chile. Valdivia, Chile

Firpo, Meri T. (Cell Biology and Genetics). B.A. 1984, Carroll College. Stockton, California

Flores-Rozas, Hernan (Molecular Biology). B.A. 1987, M.S. 1989, University of Concepcion. Valparaiso, Chile

Ford, Renee D. (Cell Biology and Genetics). B.S. 1989, Simmons College. Sanford, Maine

Fuortes, Michele (Cell Biology and Genetics). M.D. 1979, University of Rome. Rome, Italy

Gannon, Maureen (Cell Biology and Genetics). B.S. 1985, Molloy College; M.S. 1988, Adelphi University. Queens, New York

Garepapaghi, Mohammad A. (Immunology). B.A. 1987, Bowdoin College of Maine. Meiandoab, Iran

Geisberg, Mark S. (Immunology). B.S. 1985, Yale University. Leningrad, USSR

Ghosh, Rita (Molecular Biology). B.S. 1977, M.S. 1980, Delhi University. Stuttgart, Germany

Giarre, Marianna (Cell Biology and Genetics). B.S. 1987, M.S. 1989, University of Geneva (Switzerland). Araraquara, Brazil

Glickstein, Lisa J. (Immunology). B.S. 1987, Cornell University. Summit, New Jersey

Grün, Felix (Immunology). B.A. 1987, Girton College, Cambridge University (England). Frankfurt, Germany

Güre, Ali (Immunology). M.D. 1988, University of Ankara. Ankara, Turkey

Hagler, Jeremiah (Molecular Biology). B.A. 1987, University of California at Santa Cruz

Hahn, Mounou (Molecular Biology). B.S. 1985, University of Wisconsin, Seoul, Korea

Hahn, Soonjung Lucia (Molecular Biology). B.S. 1983, Seoul National University; M.S. 1985, University of Wisconsin. Seoul, Korea

Halaby, Issam (Neuroscience). B.S. 1987, American University of Beirut. Beirut, Lebanon

Han, Jihong (Biochemistry). B.S. 1987, M.S. 1989, Nankai University. Anhui Province, P. R. China

Ho, Chong-Kiong (Molecular Biology). B.A. 1990, Rutgers University. Yokohama, Japan

Hom, Judith Seuk Han (Pharmacology). B.S. 1990, Cornell University. New York, New York

Hong, Guangyuan (Molecular Biology). B.S. 1982, M.S. 1985, Peking University. Guangzhou, P. R. China

Hsu, Katharine (Cell Biology and Genetics). B.S. 1987, Stanford University; M.S. 1987, Standord University. Sacramento, California

Huang, Chin-shiou (Biochemistry). B.S. 1982, Kaohsiung Medical College; M.S. 1984, National Tsing Hua University. Hsinchu, Taiwan, Republic of China

Huang, Eric Jinsheng (Molecular Biology). B.M. 1986, National Taiwan University. Taichung, Taiwan, Republic of China

Huang, Hsien-Bin (Biochemistry). B.S. 1984, M.S. 1986, National Taiwan Normal University. Kaohsiung, Republic of China

Huber, Louise Julie (Cell Biology and Genetics). B.S. 1985, Boston University. Boston, Massachusetts

Huh, Sungoh (Neuroscience). B.S. 1984, M.S. 1987, Seoul National University. Seoul, Korea

Ince, Tan (Pharmacology). M.D. 1988, Hacettepe University of Medicine. Aydin, Turkey

Jen, Yale I-E. (Molecular Biology). B.S. 1979, National Taiwan University; M.S. 1982, Louisiana State University. Taipei, Taiwan, Republic of China

Johnson, Ellen L. (Molecular Biology). B.A. 1983, Oberlin College. Tarpon Springs, Florida

Kane, Eileen M. (Molecular Biology). B.A. 1985, Hunter College. New York, New York

Kim, Karl H. S. (Neuroscience). B.S. 1989, Michigan State University. Seoul, Korea

Kim, Sung Sub (Molecular Biology). B.S. 1986, M.S. 1988, Seoul National University. Seoul, Korea

Lander, Harry (Biochemistry). B.S. 1987, State University of New York at Stony Brook. New York, New York

'Lee, Jin-Moo (Neuroscience). B.A. 1985, Yale University. Seoul, Korea

Lee, Seong-Wook (Molecular Biology). B.S. 1985, M.S. 1987, Seoul National University. Seoul, Korea

Le Gall, Annick H. (Cell Biology and Genetics). B.S. 1990, University of California, Los Angeles. Palo Alto, California

Leonard, Christopher J. (Microbiology, Immunology, and Pathology). B.S. 1985, Cornell University. Princeton, New Jersey

Li, Dangsheng (Molecular Biology). B.S. 1988, University of Science and Technology of China. Yan Chen City, P. R. China

Li, Hailong (Molecular Biology). B.S. 1987, Beijing University. Beijing, P. R. China

Li, Mingxia (Pharmacology). B.S. 1982, Beijing Second Medical College; M.S. 1985, Chinese Academy of Medical Sciences. Beijing, P. R. China

Liang, Feng (Molecular Biology). B.S. 1988, Peking University, Jinan, P. R. China

Lim, Lorena C. (Molecular Biology). B.S. 1979, University of the Philippines at Los Banos. Manila, Philippines

Liu, Cheng (Molecular Biology). B.S. 1982, Peking University; M.S. 1985, Capital Institute of Medicine. Tiao Zhou City, P. R. China

Liu, Min (Pharmacology). B.S. 1985, M.S. 1988, Zhongshan University. Guangzhou, P. R. China

Liu, Qing (Biochemistry). B.S. 1986, Nankai University. Tianjin, P. R. China

Liu, Su (Molecular Biology). M.D. 1982, Shanghai First Medical College. Hunan, P. R. China

Luo, Yan (Molecular Biology). B.S. 1987, Beijing Medical University. Beijing, P. R. China

Mahajan, Rohit (Cell Biology and Genetics). B.A. 1984, Swarthmore College. Addis Ababa, Eithiopia

Mahmood, Umar (Physiology and Biophysics). B.A. 1987, California Institute of Technology. Lahore, Pakistan

Manley, Geoffrey (Neuroscience). B.S. 1988, University of Kentucky. Lexington, Kentucky

Mao, Buqing (Neuroscience). B.E. 1985, M.M. 1988, Shanghai Medical University. Shanghai, P. R. China

Mayer, Alan (Molecular Biology). B.S. 1986, M.S. 1986, Emory University. Passaic, New Jersey

McDonald, William F. (Molecular Biology). B.A. 1985, University of Florida. Jacksonville, Florida

[2]McNerney, Mary Ellen (Pharmacology). B.S. 1977, M.S. 1983, St. John's University. Lackawanna, New York

[2]Moncrieff, Patrice M. (Cell Biology and Genetics). B.S. 1984, Boston College. Westwood, New Jersey

Moran, Lorraine M. (Molecular Biology). A.B. 1982, Mount Holyoke College; M.S. 1984, St. John's University. New York, New York

Morham, Scott G. (Molecular Biology). B.S. 1981, Hobart College; M.S. 1985, Texas A&M University. Tarrytown, New York

Muench, Marcus O. (Cell Biology and Genetics). A.S. 1983, College of Marin; B.S. 1986, University of California. San Francisco, California

Murakami, Monica S. (Molecular Biology). B.S. 1986, Univesity of Maryland. Yokohama, Japan

Naftzger, Clarissa (Immunology). B.A. 1985, University of California at Berkeley. Berkeley, California

Nicholson, Andrew C. (Microbiology, Immunology, and Pathology). B.S. 1973, D.V.M. 1976, Michigan State University. Bangor, Maine

Nirenberg, Melissa J. (Pharmacology). B.A. 1990, Yale University. Brooklyn, New York

O'Connell, Anne Maddock (Physiology and Biophysics). B.A. 1985, Yale University. Ann Arbor, Michigan

[1]O'Malley, Edward K. (Neuroscience). B.S. 1985, State University of New York at Stony Brook. New York, New York

Onel, Kenan (Neuroscience). B.S. 1984, M.A. 1985, Yale University. Scarsdale, New York

Onrust, Rene (Molecular Biology). B.S. 1983, M.S. 1985, University of Auckland (New Zealand). Christchurch, New Zealand

Packer, Alan (Cell Biology and Genetics). B.A. 1988, Brandeis University. New Hyde Park, New York

Peng, Hong (Molecular Biology). B.S. 1982, M.S. 1985, Institute of Zoology, Academia Sinica. Beijing, P. R. China

Ponomareff, Gregory (Molecular Biology). B.A. 1988, University of California, San Diego. Oakland, California

Prescott, John (Molecular Biology). B.S. 1985, Cornell University. Minneapolis, Minnesota

Qiu, Wei-Qiao (Molecular Biology). M.D. 1982, Peking Medical College. Beijing, P. R. China

Ramakrishna, Naren R. (Cell Biology and Genetics). B.A. 1985, Johns Hopkins University. Bangalore, India

Rempel, Rachel E. (Cell Biology and Genetics). B.Sc. 1986, University of Toronto (Canada). Oxford, England

Roberts, Gretchen D. (Cell Biology and Genetics). B.S. 1976, George Washington University. New York, New York

Rochester, S. Craig (Cell Biology and Genetics). B.A. 1989, Washington and Jefferson College. Pittsburgh, Pennsylvania

Romanienko, Peter John (Molecular Biology). B.S. 1990, Fairleigh Dickinson University. East Orange, New Jersey

Romanski, Lizabeth M. (Neuroscience). B.A. 1985, Rutgers University. Fort Worth, Texas

Roth, Adam S. (Cell Biology and Genetics). B.A. 1987, University of Pennsylvania. Cleveland, Ohio

Roy, Nita (Molecular Biology). B.A. 1987, Hood College. Calcutta, India

Rubin, Brian (Molecular Biology). B.S. 1983, University of California, Berkeley. Washington, D.C.

Rubin, Lisa E. Steiner (Pharmacology). B.S. 1985, Cornell University. Baltimore, Maryland

Rudnicki, Julie (Cell Biology and Genetics). B.S. 1989, William Smith College. Buffalo, New York

Sanchez, Juan Pablo (Molecular Biology). Licenciado en Bioquimica 1988, Catholic University of Chile. Santiago, Chile

Sankar, Usha (Immunology). B.Sc. 1988, Kirori Mal College, Delhi University; M.Sc. 1990, Madurai Kamaraj University (India). Tenkasi, Tamil Nadu, India

Schlemmer, Scott (Pharmacology). B.S. 1987, Bowling Green State University. Canton, Ohio

Seo, Yeon Soo (Molecular Biology). B.S. 1982, M.S. 1984, Seoul National University (Korea). Kyung Sanynamdo, Korea

Shen, Bin (Molecular Biology). B.S. 1988, Peking University. Beijing, P. R. China

Sherwood, Peter (Molecular Biology). B.S. 1985, Cornell University. Endwell, New York

Smith, Cynthia (Cell Biology and Genetics). B.A. 1987, Johns Hopkins University. Indiana, Pennsylvania

Spector, Mona (Molecular Biology). B.S. 1980, Brooklyn College. New York, New York

Steinberg, Douglas J. (Neuroscience). A.B. 1980, Princeton University. Brooklyn, New York

Stella, Gregory (Immunology). B.S. 1987, University of Michigan. Detroit, Michigan

Stole, Einar (Biochemistry). B.S. 1986, University of Washington. Seattle, Washington

Strieter, Jon W. (Physiology and Biophysics). A.B. 1985, Princeton University. Brooklyn, New York

Stukenberg, Peter Todd (Molecular Biology). B.S. 1986, Colgate University. Syracuse, New York

Suldan, Zalman L. (Cell Biology and Genetics). B.A. 1989, University of Pennsylvania. Pittsburgh, Pennsylvania

Szabó, Anikó (Neuroscience). M.D. 1982, Szeged University Medical School. Szeged, Hungary

Taddie, John A. (Molecular Biology). B.S. 1986, Pennsylvania State University. Indiana, Pennsylvania

Tam, Wayne (Cell Biology and Genetics). B.A. 1988, Johns Hopkins University. Hong Kong

Tantravahi, JogiRaju V. (Molecular Biology). B.A. 1984, Columbia University. Boston, Massachusetts

Taylor, Alice (Immunology). B.S. 1985, Eastern Washington University. Akron, Ohio

Tougu, Killu (Molecular Biology). Tartu University (USSR). Talinn, Estonia (USSR)

Tumang, Maria A. Tancinco (Immunology). B.S. 1988, State University of New York at Stony Brook. Cebu, Philippines

*Tusie, Maria Teresa (Cell Biology and Genetics). B.S. 1979, M.D. 1985, National University of Mexico. Mexico City, Mexico

Vaughan, Kevin (Cell Biology and Genetics). B.A. 1984, Hamilton College; M.S. 1986, State University of New York at Buffalo. Buffalo, New York

Vaughan, Patricia S. Studwell (Microbiology, Immunology, and Pathology). B.S. 1984, State University of New York. Greenwich, Connecticut

Vodovotz, Yoram (Immunology). B.S. 1988, University of Wisconsin. Ramat Gan, Israel

Walewski, Jose L. (Pharmacology). B.S. 1980, Pennsylvania State University; M.A. 1984, Boston University. Caracas, Venezuela

Wang, Xin (Molecular Biology). B.S. 1987, Peking University; M.S. 1990, Peking Union Medical College. Guilin, P. R. China

Weinstock, Peter H. (Immunology). B.A. 1989, Columbia College. New York, New York

Weiser, Michael (Neuroscience). B.A. 1987, University of Vermont. Brooklyn, New York

White, Thomas M. (Physiology and Biophysics). B.A. 1989, Oberlin College. Washington, D.C.

Wittschieben, John (Molecular Biology). B.A. 1990, Colgate University. Manhasset, New York

Wu, Bin (Cell Biology and Genetics). B.S. 1987, Wuhan University. Haian, P. R. China

Xiao, Hui (Molecular Biology). B.S. 1987. Beijing University. Beijing, P. R. China

Xu, Yang (Pharmacology). B.M. 1985, Zhejiang Medical University. Zhejiang, P. R. China

Xu, Yiqing (Immunology). B.M. 1988, Shanghai Medical University. Shanghai, P. R. China

Xue, Ninrong (Neuroscience). M.D., M.S. 1988, Peking Union Medical College. Shanghai, P. R. China

Yaari, Hana (Pharmacology). B.S. 1987, University of Southern California. Jerusalem, Isarael

Yang, Yingzi (Molecular Biology). B.S. 1988, Fudan University. Nanjing, P. R. China

Yee, Frances (Neuroscience). B.A. 1987, Wesleyan University. New York, New York

Yee, Nelson Shu-Sang (Molecular Biology). B.S. 1987, Massachusetts College of Pharmacy and Allied Health Sciences. Hong Kong

[1]Yokoyama, Midori (Neuroscience). B.A. 1983, Pacific Lutheran University; M.S. 1985, Stanford University. Tokyo, Japan

Zananiri, Rami (Neuroscience). B.A. 1990, Adelphi University. Cairo, Egypt

Zavitz, Kenton H. (Molecular Biology). B. Sc. 1986, University of Toronto. Niagara Falls, Ontario, Canada

Zebala, John A. (Molecular Biology). B.S. 1986, University of Southern California. Thousand Oaks, California

Zhu, Yuanshan (Pharmacology). B.A. 1978, M.D. 1982, Hunan Medical College. Changsha, P. R. China

Candidates for the Degree of Master of Science

Continuing Students

Folger, Paula A. (Cell Biology and Genetics). B.A. 1986, University of California at Santa Cruz. Pawtucket, Rhode Island

[3]Fu, Yiping (Immunology). B.M. 1988, Beijing Medical University. Beijing, China

Martinez, Juan (Physiology and Biophysics). B.S. 1990, Tulane University. Santurce, Puerto Rico

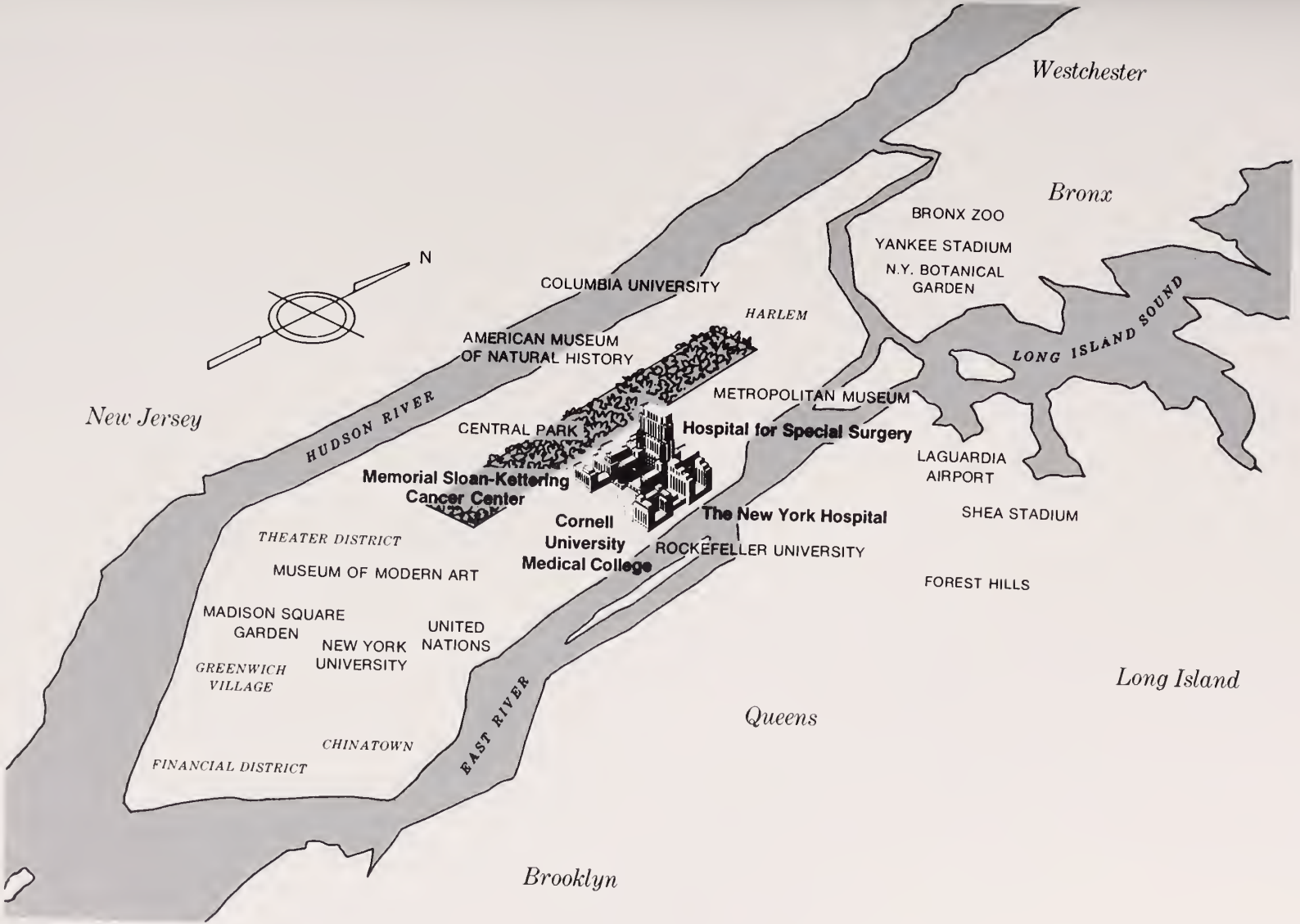
Mullings, Suzanne (Cell Biology and Genetics). B.A. 1989, Hunter College. Jamaica, West Indies

Schadlow, Valerie (Cell Biology and Genetics). B.S. 1989, Cornell University. Bologna, Italy

[1]in absentia
[2]leave of absence
[3]candidate for degree only

Index

Next page: Manhattan's East Side, with New York Hospital-Cornell Medical Center, Memorial Sloan-Kettering Cancer Center, and The Rockefeller University.


Westchester
Bronx
BRONX ZOO
YANKEE STADIUM
N.Y. BOTANICAL GARDEN
LONG ISLAND SOUND
N
COLUMBIA UNIVERSITY
HARLEM
AMERICAN MUSEUM OF NATURAL HISTORY
METROPOLITAN MUSEUM
New Jersey
HUDSON RIVER
CENTRAL PARK
Hospital for Special Surgery
LAGUARDIA AIRPORT
Memorial Sloan-Kettering Cancer Center
Cornell University Medical College
The New York Hospital
SHEA STADIUM
THEATER DISTRICT
ROCKEFELLER UNIVERSITY
MUSEUM OF MODERN ART
FOREST HILLS
MADISON SQUARE GARDEN
UNITED NATIONS
NEW YORK UNIVERSITY
GREENWICH VILLAGE
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